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THE COMPARATIVE ANATOMY AND PHARMACOLOGY OF THE PITUITARY GLAND OF UNUSUAL "EXPERIMENTAL" ANIMALS*

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CERTAIN of the recent advances in obstetrics and gynecology can justly be ascribed to the practical application of observations first made on laboratory animals by workers in the biologic sciences. One may refer to the researches being carried out at the Carnegie Institute of Embryology and at the Yale Laboratory of Primate Biology, where a number of investigators are making a cooperative study of the sexual cycle and the embryology of monkeys and apes. Because of certain similarities between these species and man, the information gained through these investigations contributes greatly to our understanding of the physiology of the gonads and of the development of the human embryo.[1]

Another striking example of application of experimental data to clinical needs is the introduction of pituitary liquid into obstetrics and medicine.

Dale, in 1906,[2] in a paper dealing with the pharmacologic actions of ergot preparations on the uterus, mentions the fact that he observed a constrictor effect with posterior pituitary preparations. Three years later he published a more detailed report of this observation. However, in the meanwhile his preliminary announcement had suggested to Blair Bell the practical value of this observation, and after some further experimental studies Bell and Hofbauer became the first to use posterior pituitary in obstetrics.[3]

A third example is the observation by Aschheim and Zondek that the urine of pregnant women contains a gonadotropic substance. This discovery was used in the development of a test for pregnancy, and at present the Aschheim-Zondek test and the Friedman test are widely used diagnostic procedures.[4]

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The above cited examples had an immediate practical application to obstetrics and gynecology. However, there are many instances in which fundamental research work has been valuable not because of its immediate practical application but because of advancing knowledge or setting at rest controversial topics. Our researches here presented fall in this latter category.

The subject to be discussed can best be approached in the form of a question: Where is the site of formation of the powerful posterior pituitary hormones, present in extracts, such as pituitrin or pituitary liquid, which are so extensively and successfully used in clinical practice? It is a remarkable fact that here we have an extract which has been available for clinical use for a number of years, and yet some of the most fundamental questions connected with the active constituents of the extract have remained either unanswered or have been the subject of considerable controversy.

In attempting to isolate principles as chemical entities, it is desirable to know whether one or several active principles are being dealt with. This in turn raises the question as to the site of origin of these principles. We could not find an answer to either of these two questions. The literature was very confused. The leading authorities in the field, such as Harvey Cushing, Dean Lewis, and Sir Humphrey Rolleston,[5] maintained vigorously that the neural lobe of the pituitary gland, being made up essentially of neuroglia tissue, did not have secretory capacity, and therefore the hormones had to be formed either from cells of the pars intermedia or from breakdown products of these cells. Close scrutiny of the evidence in support of this view made it apparent that further experimental work was needed to reach a decision. The ordinary laboratory animals were quite unsuitable for this research because in them the neural and intermediate lobes are so intimately connected that no clear-cut separation is possible. We, therefore, had recourse to a procedure which has been most productive in the solution of complex biologic questions and of which physiologists, pharmacologists, and anatomists have availed themselves; namely, the comparative approach.

We searched the literature for species in which the three lobes of the pituitary gland were either quite distinct or easily separable; or, failing this, in which the gland was rearranged in such a way that the neural lobe would not be admixed with either the intermediate or anterior lobe. We found a clue in a paper published by Wislocki on the pituitary gland of the porpoise.[6] He showed that the gland of this species had no distinct pars intermedia, and that the neural lobe was completely separated from the anterior lobe by a thick fold of dura. Our first efforts to obtain porpoise pituitaries were unsuccessful, and therefore we turned our attention to the collection of pituitary glands from whales.

Through the cooperation of the Consolidated Whaling Company, we were permitted to visit their two stations on the Queen Charlotte Islands in British Columbia, where we obtained glands from the sperm, finback,

blue, and humpback whales. Glands from the white whale were collected at Point Lebel on the St. Lawrence River, and during the summer of 1939 we were fortunate in securing glands from two species of porpoise, the speckled and the bottle-nosed, through the courtesy of the Marine Studios in St. Augustine, Florida. In all instances the glands were fixed for both histologic and pharmacologic purposes.*

The hypophyses of the various species of whales and porpoises are essentially similar[7] and consist of a large flattened anterior lobe, a comparatively small neural lobe, and a well-developed pars tuberalis. There is no macroscopic or microscopic evidence of a pars intermedia. The anterior and neural lobes are completely separated by a thick dural septum and by the pia-arachnoid which encases the neural lobe.

The anterior lobe is composed of the characteristic nests of chromophobe and chromophil cells supported by a network of vascular connective tissue. The pars tuberalis is also well-vascularized and consists of small pale-staining cells and occasional colloid-filled vesicles. The neural lobe, for the most part, is made up of nerve fibers and pituicytes. The blood supply is rich and Herring bodies are scattered throughout the lobe. Nerve cells are present in the neural lobe of the porpoise but are not numerous.

It is apparent, therefore, that the anatomic relations of the cetacean hypophysis are such as to permit complete separation of the anterior and neural lobes, so that extracts may be prepared from either lobe without admixture of the other. For this purpose, the glands were removed as soon after the death of the animal as possible and the separated lobes placed in acetone to dehydrate and to defat them. They were then ground up into a fine powder and extracted with 0.25 per cent acetic acid, so that 1 c.c. of the extract contained the activity in 1 mg. of dried powder. The extracts were then assayed for their melanophore-dispersing, oxytocic, pressor, and antidiuretic activities by the standard techniques. All preparations were compared with the international standard powder.

The results of these experiments indicate that extracts of the neural lobe contain oxytocic, pressor, and antidiuretic activity but no melanophore-dispersing activity. Extracts of the anterior lobe, on the other hand, contain considerable melanophore-dispersing activity but only doubtful traces of pressor, antidiuretic, and oxytocic activity. Extracts of the pars tuberalis, which probably include portions of the neural stalk, contain varying amounts of all four activities.[8, 9]

While the work on the cetacean hypophysis was in progress, search was made for other species which have no discrete pars intermedia. The description by de Beer[10] and others indicated that this lobe is

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lacking in birds, and from Mrs. Lewis of the Carnegie Institute of Embryology, we learned that a similar condition exists in the armadillo hypophysis. In consequence, pharmacologic and anatomic studies were carried out on the chicken hypophysis by DeLawder, Tarr and Geiling,[11] and on the armadillo hypophysis by Oldham.[12] The absence of a pars intermedia in both these species was confirmed, and the complete separation of anterior and neural lobes by collagenous connective tissue was established. Furthermore, assays of the separated lobes of both chicken and armadillo show that the melanophore-dispersing hormone is confined to the anterior lobe, and the oxytocic, pressor, and antidiuretic hormones to the neural lobe. Essentially similar results were obtained by Oldham, McCleery, and Geiling in the hypophysis of a South American manatee.[13]

Assays of different areas of the anterior lobes of cetaceans and the armadillo indicate that the melanophore-dispersing hormone is present in higher concentration in the cephalic than in the caudal (juxtaneural) region.[14] This is in agreement with the preliminary findings of DeLawder, Tarr and Geiling[11] in the chicken which were later confirmed by Kleinholz and Rahn.[15] An investigation is now in progress to determine the first appearance of the hormone in the hypophysis of the developing chick embryo. We have already determined its presence in chicks of five days which is considerably in advance of any cellular differentiation in the anterior lobe.

Having been assured of the absence of the pars intermedia in the adult cetaceans, armadillo, and chicken, it was of importance to study the embryologic development of the glands in these species to determine whether a pars intermedia is present at any time during development. It will be recalled that in the human being, many authorities maintain that a discrete pars intermedia is lacking. However, studies of the developing human hypophysis such as those of Atwell[16] and of Tilney[17] prove conclusively that this portion is present during development and childhood, although it may become greatly reduced in the adult.

We were able to secure a representative series of armadillo embryos and the results of this study are now in press.[18] In brief, it was found that the anterior and neural lobes are at all times completely separated by either a thick basement membrane or by vascular mesenchyme. Furthermore, while the caudal or juxtaneural wall retains its columnar epithelial appearance until development is fairly well advanced, in the later stages it becomes invaded by vascular connective tissue which breaks the cells up into the typical cell nests of the anterior hypophysis. Hence, at the time of birth, the lumen of Rathke's pouch has practically disappeared and the cephalic and caudal regions of the anterior lobe are essentially similar.

The collection of cetacean embryos is naturally a more difficult problem. However, we have been fortunate to secure a number of specimens, the pituitaries of which have been serially sectioned. In all, the anterior and neural lobes are completely separated by a thick septum of connective tissue. Only in the smallest embryos can the residual lumen be seen and in these the caudal or juxtaneural portion

of the anterior lobe is similar in structure to the anterior region. Hence, we believe that in both the whale and the armadillo there is at no time during development a discrete pars intermedia comparable to that found in most other species.

DISCUSSION

Our studies on the site of elaboration of the oxytocic, pressor, and antidiuretic hormones receive ample support from the work of Fisher, Ranson, and Ingram.[19] In an extensive series of experiments, these investigators produced diabetes insipidus in cats and monkeys by lesions in the region of the supraoptic nuclei. Examination of the pituitary glands of these animals reveals degeneration of the supraopticohypophyseal tracts and atrophic changes in the pituicytes and loss of pressor, oxytocic, and antidiuretic activity. The anterior and intermediate lobes on the other hand are apparently unchanged, and there is no loss of melanophore-dispersing activity. Changes in the pituicytes have also been reported by Wang[20] and collaborators, following liberation of pressor, antidiuretic, and oxytocic activities by stimulation of the afferent vagus.

Gersh[21] has recently described changes in the "parenchymatous" cells of the neural lobe (pituicytes) in response to a need for water conservation within the body, and he correlates these structural differences with changes in hormone content. While we have not applied Gersh's histologic methods to our material, nevertheless we did obtain some evidence that in the porpoise the hormone content is lowered in animals deprived of their food, which is the main source of metabolic water in cetaceans.[22]

The possibility that the rich supply of nerve fibers in the neural lobe plays a role in the elaboration of the active principles has been advanced by Rasmussen,[23] but as Griffiths[24] has pointed out, the fact that the active principles may be recovered from tissue cultures of the neural lobe [25, 26] does not support this contention, since in these experiments the nerve fibers have lost their connection with their cells of origin in the supraoptic nuclei. It is apparent, however, that more attention must be directed toward the histophysiology of the neural lobe before the final decision is reached as to the precise method of secretion of the active principles. This will undoubtedly necessitate the use of some other method than the capricious silver-staining techniques that most investigators have employed.

Since it is now accepted that all cells are capable of elaborating substances which may or may not play a physiologic role, there need no longer be any hesitancy in ascribing secretory function to cells of nervous origin. The work on the humoral transmission of nervous impulses indicates that powerful pharmacodynamic principles may be liberated at nerve endings. Furthermore, the cells of the adrenal medulla which are responsible for the formation of epinephrine have their origin in the neural crest. There seems, therefore, no reason to believe that the intrinsic elements of the neural lobe are incapable of giving rise to the oxytocic, pressor, and antidiuretic hormones.

DOES THE NEUROHYPOPHYSIS HAVE AN ENDOCRINE FUNCTION?

Despite the very striking pharmacodynamic effects of extracts of the neurohypophysis, information concerning either its physiologic or pathologic role lacks finality. It may be of interest to compare the anterior and neural lobes of the hypophysis on the one hand with the cortical and medullary portions of the adrenal on the other, as appears in Table I.

TABLE I. COMPARISON OF PITUITARY AND ADRENAL GLANDS

Pituitary		Adrenal
Anterior lobe	Typical endocrine structure	Cortex
	Function and effects of extracts: Somatic and metabolic Complex interrelationship with other glands Number of hormones uncertain Effects of extracts slow in onset	
Intermediate lobe	Function in mammals unknown Regulator of melanophore cells in lower forms	------
Neural lobe	Cells of nervous origin	Medulla
Neuroglia cells	Powerful hormones	Chromaffin tissue
	Pressor Antidiuretic Oxytocic	Epinephrine
	Effects of extracts prompt and of short duration Action chiefly on smooth muscle structures Role in animal economy still debatable	

Injection of neural lobe extracts causes striking changes in the cardiovascular, respiratory, and renal systems, the gastrointestinal tract, and the uterus. These effects are precipitous in onset and of short duration. While many of these changes are effected only by doses larger than could be considered physiologic, nevertheless they do furnish suggestive evidence of the possible functions of the neural hypophysis.

THE POSTERIOR PITUITARY AND WATER METABOLISM

Of the possible physiologic functions ascribable to the hormones of the neurohypophysis, the regulation of water metabolism seems best established from both the experimental and clinical approaches. Fisher, Ingram, and Ranson, and others[19, 27] have shown that injuries resulting in the destruction of the supraopticohypophyseal tracts in laboratory animals result in diabetes insipidus which can be alleviated not only by injection of small amounts of the pressor fraction of the posterior pituitary but also by removal of the anterior lobe. These workers point out that the failure by a number of workers to produce diabetes insipidus may be due either to the fact that both lobes were removed or to incomplete destruction of the neural hypophysis, since it appears that functioning neural lobe tissue extends dorsally for some distance into the median eminence.[28] Clinical evidence of the

role of the neurohypophysis in diabetes insipidus is available in such reports as those of Berblinger,[29] Biggart,[30] and Baker and Craft,[31] in which post-mortem examination revealed either total destruction of the pars nervosa or degenerative lesions in the supraopticohypophyseal tracts accompanied by atrophic changes in the pars nervosa.

A POSSIBLE METABOLIC ROLE OF THE POSTERIOR PITUITARY

We found that certain well-defined circulatory and respiratory changes are elicited by the intravenous injection in dogs or the intramuscular injection into human beings of moderate doses of posterior pituitary extract or of the pressor fraction, pitressin.[32, 33]

In dogs the following series of events are noted: For a brief period (five to ten minutes) immediately following the administration of the drugs, the venous blood draining the limbs becomes arterial in color and shows a high oxygen content, a rapidly rising lactic acid concentration, and a concomitantly lowered carbon dioxide content. There is at the same time a precipitous decrease in total oxygen consumption and a lowering of the cardiac output. In the immediately ensuing recovery period, which persists for one and one-half to two hours after the injection, the physiologic picture is reversed. An abnormally dark venous blood is found, indicating increased oxygen utilization by the "starved" tissues; a further rise in lactic acid is followed by a gradual return to the pre-injection level; the carbon dioxide content returns slowly to a slightly subbasal value. Total oxygen consumption and cardiac output show parallel increases above their pre-injection values and then gradually return to the basal level. In normal human subjects essentially similar changes are produced by the intramuscular injection of the above named preparations.

The changes induced by the oxytocic fraction, pitocin, are not as clear-cut as those produced by pitressin. Nevertheless, in appropriate doses purified pitocin causes a definite increase in oxygen consumption. Thus pitressin and pitocin have, in a sense, antagonistic actions.

It is clear from these facts that the extracts of the posterior pituitary gland, when injected into the body, can act rapidly and efficiently in regulating the exchange of metabolites between blood and tissues. Assuming that the extracts used represent the hormone as it functions in the body, then after the injection of even small doses of the extracts there would result a concentration of the hormone in the blood greater than under normal conditions. Whether the physiologic changes induced by such concentrations can be regarded as an exaggerated hormonal effect, or would be produced by any substance acting either through the capillary constrictor effect or directly on the tissue cells remains uncertain. Until these points are settled one can do no more than propose the following hypothesis: If we postulate that the action of the extracts represents that of the posterior pituitary hormone as it exists in the body, and that the injection of such extracts, although it be a crude imitation under exaggerated conditions, simulates the normal action of the hormone, then the posterior lobe of the hypophysis functions in the body as one of the regulators of metabolism.

Furthermore, one could conceive that while the pressor and oxytocic hormones have, in a sense, opposite actions, they may function in an harmonious way within the body to bring about the regulation as stated.

THE POSTERIOR HYPOPHYSIS AND PARTURITION

A question of special interest to gynecologists and obstetricians is whether the oxytocic principle of the posthypophysis plays a role in parturition. This subject has been reviewed recently by both Snyder[34] (1938) and by Reynolds[35] (1939). We agree with Snyder in his conclusion that the evidence on hand does not rule out the oxytocic hormone as a factor in normal parturition. The early failures to prevent parturition by removing the posterior lobe or severing the stalk must be reinterpreted in the light of more recent work which indicates that the characteristic structure of the neurohypophysis extends into the median eminence, hence all functioning posthypophyseal tissue was probably not removed by the early workers.

Of special significance is the recent report by Fisher, Magoun, and Ranson[36] that dystocia occurred in 7 cats in which diabetes insipidus had been induced by the destruction of the supraopticohypophyseal tract. Furthermore, Haterius and Ferguson[37] obtained contraction of the uterus by stimulation of the infundibular stalk. However, such contractions did not occur after electrolytic lesions were placed in the stalk.

Gersh[21] reports a cellular hypertrophy in the neurohypophysis of the rat during or slightly after parturition which he believes to be correlated with hormone secretion; nevertheless, he points out that this may be attributable either to an increase in oxytocic hormone to assist in expulsion of the fetus or to an increased output of antidiuretic hormone to preserve the body fluid from excessive loss by the demands incidental to parturition (e.g., shedding of placenta, milk formation, and increased blood pressure).

According to Reynolds, the work of Fisher and his associates is open to the criticism that the anterior lobe was apparently also affected, since the animals did not subsequently go into estrus; while in regard to the work of Haterius and Ferguson, he suggests that the increased motility may be secondary to a transiently improved circulation.

That the sensitivity of the human uterus to posterior pituitary undergoes marked changes during both pregnancy and the menstrual cycle has been shown by Knaus,[38] Robson,[39] Adair and Haugen,[40] and others. It is generally agreed that in many species, including the human being, the sex hormones are an important factor in the alterations in sensitivity of the myometrium to pituitrin. The fact that the corpus luteum hormone inhibits the contractions, normally initiated by pituitrin, has been used to explain the refractiveness of the uterus during early pregnancy. Estrone, on the other hand, increases the sensitivity of the uterus to pituitrin, and hence it has been suggested that the increased amount of estrin in the circulating blood towards the end of pregnancy acts in conjunction with the oxytocic hormone in the initiation of labor. While this hypothesis is an attractive one, it is obvious that further evidence is required before the posterior pituitary can be ascribed with certainty as a physiologic role in parturition.

POSTERIOR PITUITARY AND ECLAMPSIA

The fact that the vascular and renal changes produced by injections of posterior lobe preparations into animals and man resemble so closely the signs and symptoms of eclampsia or pre-eclampsia prompted the suggestion that these baffling disease entities might be due to hyperfunction of the neurohypophysis. Numerous attempts have been made to demonstrate the presence of the pressor or oxytocic hormones in the blood of such patients. Positive findings were reported by Anselmino and Hoffmann[41] (1931), but their results have not been confirmed by later workers such as Byrom and Wilson,[42] and Melville.[43] The possibility remains that the tissues of the pre-eclamptic or eclamptic patients may be unusually sensitive to the posterior lobe hormones. This postulate receives support from the work of Dieckmann and Michel,[44] Lambillon and Schockaert,[45] and of deValera and Kellar,[46] who found that eclamptic or pre-eclamptic patients responded to injections of pitressin with a rise in systolic blood pressure and a marked decrease in urine volume, whereas normal pregnant women were relatively insensitive. Dieckmann and Michel[44] believe that their results have a double implication: "(1) The injection of pituitrin per se may be dangerous in toxemic patients even in small amounts . . . . (2) Pituitary extract in minute doses offers a good test in differentiating pre-eclampsia from vascular-renal disease in pregnancy."

From this brief discussion it is evident that additional research will be necessary before the neurohypophysis can be assigned an etiologic role in the toxemias of pregnancy.

MISCELLANEOUS EFFECTS OF POSTERIOR PITUITARY EXTRACTS

Extracts of the pressor hormone of the posterior pituitary usually stimulate the smooth muscle of the large intestine, and therefore such preparations have been used to restore intestinal tone postoperatively. In much larger doses, they lead to gastric erosion in the region of the hydrochloric acid secreting cells of the stomach (Dodds, Noble and Smith, 1934[47]). This effect appears to be due to local ischemia resulting from vasoconstricting action of the pressor hormone. However, the high doses required to produce these lesions make it improbable that the neurohypophysis plays a role in the etiology of gastric ulcers.

Dodds[48] and his associates have shown that large doses of posterior pituitary extract lead to anemia which, they thought, was due to an increased blood destruction. Gilman and Goodman,[49] on the other hand, believe the anemia to be due to hemolysis of the cells arising from a dilution of the blood as a result of increased water retention. It is of interest to record that Noble, Rinderknecht and Williams[50] have recovered material possessing pressor and antidiuretic activity from a patient suspected of having hyperfunction of the posterior pituitary. The symptoms of this patient were described by Jones[51] and included hypertension, hyperchromic microcytic anemia, achlorhydria, and abnormal carbohydrate metabolism. For a more detailed account of the possible pathologic effects of hypersecretion of the posterior lobe reference should be made to the excellent summary by Liu.[52]

SUMMARY OF CONCLUSIONS

The complete separation of the anterior and neural lobes of the hypophysis of cetaceans, the armadillo, the chicken, and the South

American manatee, is such as to render diffusion of the active principles from one lobe to the other highly improbable. Furthermore, Wislocki[53] and his associates, in studies on the vascular system of the hypophysis, have shown that the blood supply of the anterior and neural divisions is practically independent, hence it is highly improbable that the active substances could be transported from one lobe to the other via the blood stream. Thus the presence of oxytocic, pressor, and antidiuretic hormones in the neural lobe of the above species provides indisputable evidence that these substances are elaborated by the intrinsic elements of the neural lobe, and therefore the older viewpoint that they arise from the cells of the pars intermedia can be rightly abandoned.

In spite of the spectacular pharmacodynamic activity of posterior pituitary extracts, we are unable to ascribe any specific function in the animal economy to the active agents of these extracts. However, experimental and clinical studies on diabetes insipidus strongly suggest that the pressor hormone is actively concerned in the regulation of water balance. A more general function in metabolism is indicated by the marked changes in the blood chemistry observed after injection of extremely small quantities of posterior lobe preparation.

The clinical use of the oxytocic activity of posterior lobe extracts is justifiably the basis for a query as to whether this substance is concerned in the physiologic mechanisms of parturition. A satisfactory answer to this question can come only after further research. This is likewise true for the hypothesis that associates eclampsia and preeclampsia with the pressor hormone of the pituitary gland.

REFERENCES

(1) *Hartman, C. G.:* Endocrinology **25:** 670, 1939. (2) *Dale, H.:* J. Physiol. **34:** 163, 1906. (3) *Bell, W. Blair:* Brit. M. J. **2:** 1609, 1909. (4) *Aschheim, S.:* Glandular Physiology and Therapy, 1935, p. 241. (5) *Rolleston, Sir H. D.:* The Endocrine Organs in Health and Disease, Oxford University Press, London, 1936, Humphrey Milford, p. 67. (6) *Wislocki, G. B.:* Arch. Surg. **18:** 1403, 1929. (7) *Wislocki, G. B., and Geiling, E. M. K.:* Anat. Rec. **66:** 17, 1936. (8) *Geiling, E. M. K.:* Bull. Johns Hopkins Hosp. **57:** 123, 1935. (9) *Valsö, J.:* Klin. Wehnschr. **13:** 1819, 1934. (10) *de Beer, G. R.:* Biologic Monographs and Manuals, **6:** Edinburgh, 1926, Oliver and Boyd. (11) *DeLawder, H. M., Tarr, L., and Geiling, E. M. K.:* J. Pharmacol. & Exper. Therap. **51:** 142, 1934. (12) *Oldham, F. K.:* Anat. Rec. **72:** 265, 1938. (13) *Oldham, F. K., McCleery, D. P., and Geiling, E. M. K.:* Anat. Rec. **71:** 27, 1938. (14) *Oldham, F. K., Last, J. H., and Geiling, E. M. K.:* Proc. Soc. Exper. Biol. & Med. **43:** 407, 1940. (15) *Kleinholz, L. H., and Rahn, H.:* Anat. Rec. **76:** 157, 1940. (16) *Atwell, W. J.:* Am. J. Anat. **37:** 157, 1926. (17) *Tilney, F.:* Bull. Neur. Inst., New York **5:** 387, 1936. (18) *Oldham, F. K.:* Am. J. Anat. In press. (19) *Fisher, C., Ingram, W. R., and Ranson, S. W.:* Diabetes Insipidus and the Neuro-humeral Control of Water Balance, Ann Arbor, 1938, Edwards Brothers, Inc. (20) *Wang, Kun-jen:* Chinese J. Physiol. **13:** 405, 1938. (21) *Gersh, I.:* Am. J. Anat. **64:** 407, 1939. (22) *Geiling, E. M. K., Vos, B. J., and Oldham, F. K.:* Endocrinology **27:** 309, 1940. (23) *Rasmussen, A. T.:* Endocrinology **23:** 263, 1938. (24) *Griffiths, M.:* Proc. Linn. Soc. N. S. W. **63:** 89, 1938. (25) *Geiling, E. M. K., and Lewis, M. R.:* Am. J. Physiol. **113:** 534, 1935. (26) *Anderson, E., and Haymaker, W.:* Proc. Soc. Exper. Biol. & Med. **33:** 313, 1935. (27) *Richter, Curt:* Proc. Assn. Res. on Nerv. & Ment. Dis. **17:** 392, 1936. (28) *Weaver, T. A., and Bucy, P. C.:* Endocrinology **26:** 920, 1940 (Advance abstract). (29) *Berblinger, W.:* Endokrinologie **20:** 305, 1938. (30) *Biggart, J. H.:* Edinburgh M. J. **43:** 417, 1936. (31) *Baker, A. B., and Craft, C. B.:* Endocrinology **26:** 801, 1940. (32) *Grollman, A., and Geiling, E. M. K.:* J. Pharmacol. & Exper. Therap. **46:** 447, 1932. (33) *Geiling,*

E. M. K., and DeLawder, A. M.: Bull. Johns Hopkins Hosp. **51:** 1 and 335, 1932. (34) *Snyder, F. F.:* Physiol. Rev. **18:** 578, 1938. (35) *Reynolds, S. R. M.:* The Physiology of the Uterus, 1939, Hocher. (36) *Fisher, C., Magoun, H. W., and Ranson, S. W.:* Am. J. Obst. & Gynec. **36:** 1, 1938. (37) *Haterius, H. O., and Ferguson, J. W. K.:* Am. J. Physiol. **124:** 314, 1938. (38) *Knaus, Hermann:* Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes, Vienna, 1934, W. Maudrich. (39) *Robson, J. M.:* Recent Advances in Sex and Reproductive Physiology, Philadelphia, 1934, P. Blakiston's Son & Co. (40) *Adair, F. L., and Haugen, J. A.:* Am. J. Obst. & Gynec. **37:** 753, 1939. (41) *Anselmino, K. J., and Hoffmann, F.:* Arch. Gynäk. **147:** 597, 1931. (42) *Byrom, F. B., and Wilson, C.:* Quart. J. Med., New Series **2:** 361, 1934. (43) *Melville, K. I.:* J. Exper. Med. **65:** 415, 1937. (44) *Dieckmann, W. J., and Michel, H. L.:* Am. J. Obst. & Gynec. **38:** 131, 1937. (45) *Lambillon, J., and Schockaert, J. A.:* Bruxelles-méd. **17:** 1468, 1937. (46) *De Valera, E., and Kellar, R. J.:* J. Obst. & Gynaec. Brit. Emp. **45:** 815, 1938. (47) *Dodds, E. C., Noble, R. L., and Smith, E. R.:* Lancet **2:** 918, 1934. (48) *Dodds, E. C., and Noble, R. L.:* Nature **135:** 788, 1935. (49) *Gilman, A., and Goodman, L.:* Nature **143:** 379, 1939. (50) *Noble, R. L., Rinderknecht, H., and Williams, P. C.:* Lancet **1:** 13, 1938. (51) *Jones, E. I.:* Lancet **1:** 11, 1938. (52) *Liu, S. H.:* Chinese Med. J. **55:** 448, 1939. (53) *Wislocki, G. B.:* Proc. Assn. Res. on Nerv. & Ment. Dis. **17:** 48, 1938.

FUNCTIONAL AND GROWTH CHARACTERISTICS OF STRUMA OVARII*

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THE story of ovarian strumas is too well known to warrant repetition. The literature was recently reviewed in great detail by Nicholson and by Neumann. The purpose of this paper is to discuss certain functional qualities of these tumors and to evaluate their clinical significance.

GENERAL CONSIDERATIONS

The histogenesis of ovarian strumas is obscure. It is simplest to accept them as regional teratomas regardless of the fact that they may represent reduced one-sided developments as in so-called pure ovarian strumas, or may be part of a totipotent development involving all three germ-layers. It is possible that they constitute the adult phase of anlage displacements, although some claim that they are the result of some obscure unorganized ovogenic development. It is reasonably certain that they are *not* the result of thyroid metastases into an ovary, since this is contrary to the behavior of metastasizing thyroid neoplasms. It also is reasonably certain that they do not represent colloid degenerations of cysts arising from the many different forms of tubular structures with which the ovary swarms. Differential staining qualities of colloid and certain morphologic stigmata of the parenchyma leave little doubt that ovarian strumas are made up of aberrant thyroid tissue.

FUNCTIONAL CHARACTERISTICS

Since 1889, when Boettlin described thyroid in a dermoid, reports of some 150 cases of ovarian strumas have found their way into the medical literature, about 40 of which have been reported in this country.† The actual incidence is not known. Casual statistics based on individual experiences place it at from 2 to 15 per cent of ovarian teratomas, mainly dermoids. We found it to be 4 per cent in our material. Since the discovery of thyroid tissue in ovaries depends entirely upon a readily recognizable tissue mass or on good luck in making a microscopic search, small strumas may be easily overlooked. It has been pointed out repeatedly that extensive microscopic studies will reveal minute areas of thyroid tissue in many ovarian teratomas, just as minute rem-

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†1904, Anspach; 1909, Frank, Wood, Norris; 1910, Proescher and Roddy; 1913, Outerbridge; 1914, Strong, Ries; 1925, Koucky; 1926, Rohdenburg, Simpson; 1928, Frankel and Lederer; 1929, Moench; 1930, Shapiro; 1931, Plaut; 1933, Masson and Mueller; 1934, Lyday; 1936, Cantor and Kogut; 1940, Wynn, McCarthy, and McClendon, Emge.

nants of other germ layers can be found in most so-called pure ovarian strumas if the search is carried far enough. In fact, Neumann recently voiced the opinion that probably there is no such thing as a pure struma ovarii. This, in itself, is of no great consequence, but what is more important is the fact that an ovarian struma (and not necessarily a very large one), under conditions yet unexplained, can seriously unbalance the metabolism of the body and at times invade other tissues through metastatic growth. According to existing reports, 8 strumas of the ovary have produced metastases, and a slightly larger number are described as having caused thyrotoxic symptoms. It is this group which attracts our attention, because we have encountered two instances of hyperthyroidism accompanying such tumors, one of which, in addition, produced extensive metastases.

Fig. 1.

Most ovarian strumas are silent unless mechanical difficulties arise, and the greatest number, by far, are not diagnosed until they reach the laboratory. In fact, most of them are discovered accidentally, either because of size or because of pedicle-twists, or in the course of routine pelvic examinations. It is common, therefore, for them to come to operation without critical metabolic studies and, as a consequence, milder types of hyperthyroidism are undoubtedly overlooked.

Since these tumors consist of various quantities of thyroid tissue it is reasonable to presume that they function like the thyroid. Very little is known about this, partly because of their rarity and partly because they seem to reach a state of functional inactivity resembling, in certain respects, colloid goiters of the thyroid. Only occasionally is a tumor encountered which is active enough functionally to disturb

metabolism, and unless such a tumor is large it can be overlooked. A patient whose case illustrates this point came under our care in 1929.

CASE 1.—G. C., a doctor's wife, 31 years old, had been treated medically for mild Graves' disease for several years. She had borne two children, with no complications, and had not been examined pelvically for several years. Her basal metabolic rate had fluctuated between plus 34 and plus 12 per cent, with various bouts of severe tachycardia. Her medical attendant reported that rest and iodine therapy had benefited, but never relieved, her. Thyroidectomy had been considered but was postponed, fortunately, because of the patient's distaste for operations. Late one night an acute attack of severe right lower quadrant pain accompanied by vomiting led to the discovery of a twisted pedicle cyst of the right ovary, considered a dermoid because of its firmness. Operation yielded a tumor 10 by 6 by 6 cm. made up of various dermoid structures which included a large island of thyroid tissue in a state of early hyperplasia (Fig. 1). Judging from the morphology alone, one would not expect such a high degree of hyperthyroidism. However, this coincides with the experience of others. In this case, toxic symptoms abated within forty-eight hours and at the end of ten days the patient was completely free from toxic manifestations. On the fourteenth day her basal metabolic rate had dropped to minus 14 per cent. Neither chemical nor biologic assays were done, but the clinical evidence is so striking and the morphologic appearance of the tissue so suggestive that there can be little doubt the thyrotoxic state was caused by this struma ovarii.

Similar observations have been reported by Moench, Kovacs, Morgen, Kleine, Aschkanasy, Cantor and Kogut, and Neumann. In each instance, hyperthyroidism was corrected by removal of an ovarian struma. Kleine and Neumann report particularly striking cases with metabolic rates of plus 30 and plus 40 per cent which were somewhat improved by medical treatment but relieved only by removal of the tumor. In none of the cases reported was the morphologic change as striking as one would expect to find had the condition been produced in the thyroid gland.

We encountered a second case recently, still more interesting because of the unusual combination of thyrotoxicosis with metastatic ovarian strumosis.

CASE 2.—R. E. B., 20 years old, primipara, white, of Russian-American extraction, came to our clinic on March 19, 1938. She had married in December, 1937, menstruated last on Jan. 28, 1938, and separated from her husband in March. Finding herself pregnant, she went to an abortionist who discovered a pelvic tumor and refused to help her. She then consulted her own physician, Dr. E. D. Torre, who directed her to us.

Menarche occurred at the age of 17, but was followed immediately by twelve months of amenorrhea, so that regular menstruation was not established until the patient was eighteen years old. Since then, the menstrual cycle has varied from twenty-one to twenty-five days, lasting three to four days, with a normal amount of flow and without discomfort. General health had been fair and uneventful, until she noticed an increasing nervous irritability.

Pelvic examination revealed a pregnancy of about two months. The uterus was pushed backward and to the left by a large right ovarian tumor of limited mobility, rising to the level of the promontory of the sacrum. General examination of the patient revealed nothing unusual except a pulse rate of 100, interpreted as an expression of anxiety. Blood studies showed a mild anemia, with 4,000,000 red cells and 86 per cent Hg, a coagulation time of five minutes, and a bleeding time of two minutes. Blood pressure registered 98/50, and the net body weight was 125 pounds. Urine studies revealed no pathology. The basal metabolic rate was not

determined at this time. The preoperative diagnosis was pregnancy of two months' duration complicated by a large ovarian tumor, probably a dermoid. Struma was not suspected.

On March 31, 1938, the abdomen was opened and a large grayish tumor of the right ovary, having the appearance of a pseudomucinous cyst, was removed. Because of the presence of reddish growths in the omentum the tumor was assumed to be malignant and pregnancy was interrupted by hysterotomy. There was no free fluid in the abdomen. Recovery was uneventful. Microscopic study revealed both the neoplasm and the metastases to be composed exclusively of thyroid tissue in a state of colloid storage, and a diagnosis of pure struma ovarii with metastases was made.

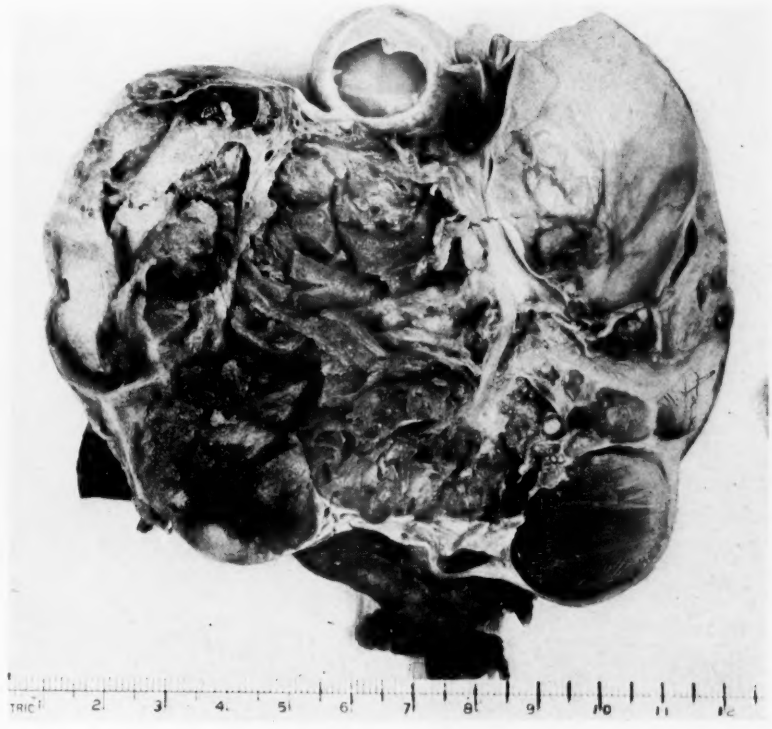

Fig. 2.

Gross Description.—The tumor, grayish pink in color, measured 14 by 11 by 11 cm., weighed 400 Gm., and was irregularly globular. The cut surface showed a multilocular formation, individual components varying from a few millimeters to 2 or 3 cm. in diameter (Fig. 2). Some of the loculi contained a clear blood-colored fluid; others were filled with soft, pink or gray, spongy substances resembling colloid. A metastasis from the omentum 2 cm. in diameter had the appearance of fresh thyroid and showed fine follicles on the cut surface.

Microscopic Study.—All pieces taken from the large tumor showed a uniform resemblance to thyroid tissue, and no other type of organized tissue was found. The general architecture was that of follicle formation, each follicle being well defined and without a basement membrane (Fig. 3). Large groups of follicles were surrounded by dense layers of smooth muscle and connective tissue bundles. A number of these groups were enclosed in a more superficial areolar layer of connective tissue, probably of ovarian origin. Follicles were lined with single layers of low cuboidal cells with large vesicular nuclei. There were no ciliae and most of the cells were of the type described as "chief cells" of the thyroid. So-called

Langendorff cells, characterized by small dark nuclei and a very low cuboidal structure made up of deep-staining cytoplasm were present, but not abundant (Fig. 4). According to staining intensities, colloid at various stages filled most of the follicles. Hyperplastic areas were scarce and free from colloid. Where present, their follicles showed infolding with frequent mitotic activities. The supporting stroma

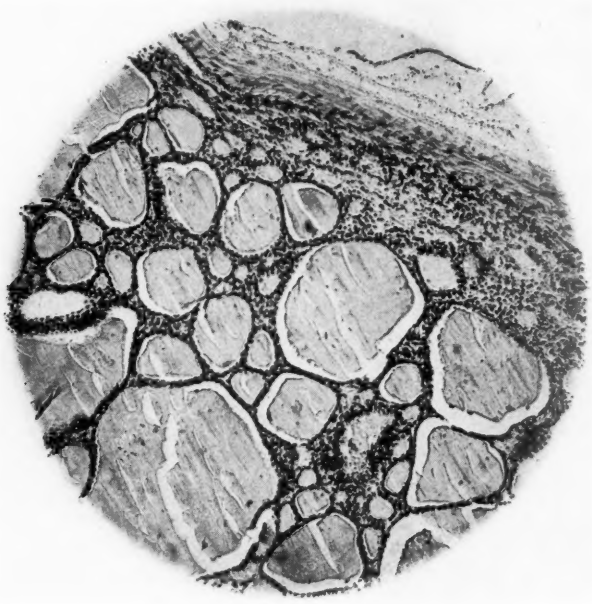

Fig. 3.

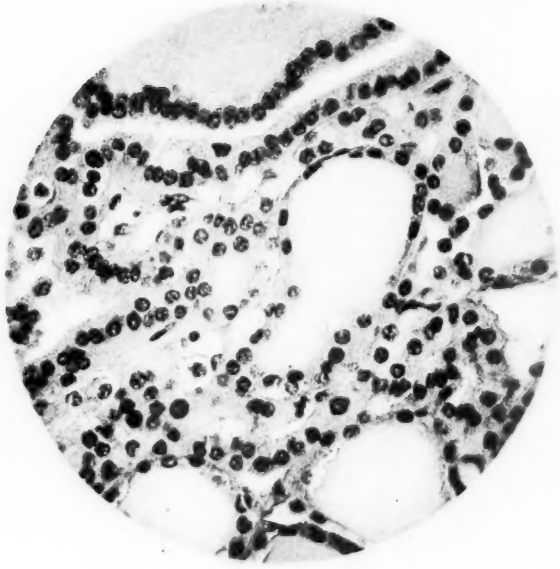

Fig. 4.

showed marked scarcity of connective tissue cells and contained free colloid. Long slender tubular follicles, probably produced by central pressure, were freqent toward the surface of the tumor (Fig. 5). Single mitotic figures were common throughout, usually located at a point where budding was taking place.

Implants from the perimetrium, the left ovary, and the omentum showed essentially the same structural architecture as the parent tumor, except that mitoses were not so evident.

On April 12, twelve days after operation, the basal metabolic rate was plus 6.3 per cent. On June 7 it had risen to plus 21.5. During the remainder of the year the patient became very nervous and lost ten pounds in weight, presenting a typical picture of Graves' disease. There was, however, no change in menstruation. The patient was then lost track of for a few months and when she reported in March, 1939, hyperthyroidism was still present but less pronounced. The basal metabolic rate was plus 16.5 per cent; there were no palpable abdominal masses and no discomfort or tenderness, and the blood picture had not changed. Because of the persistence of toxic symptoms, removal of omental metastases was recommended.

Fig. 5.

On March 22, 1939, all of the greater omentum (harboring many aberrant thyroids), with as much of the lesser omentum as was feasible, and some large nodules along the colic flexures, were removed. Altogether, there were probably between 50 and 60 smooth, firm, well-organized nodules which resembled normal thyroid tissue in color and texture. They varied from a few millimeters to 3 or 4 cm. in diameter. Each nodule was olive-shaped, and each was attached to the underlying structure by a thin pedicle carrying a well-developed vein and a small artery (Fig. 6). There was no sign of invasion of the adjacent structures, and no ascites. There were numerous other nodules along the lateral aspects of the ascending and descending colon, a few on the superior surface of the transverse colon, and a few along the parietal peritoneum over the bladder, the left ovarian ligament, and in the cul-de-sac. Deep-seated nodules could be felt in the mesentery of the sigmoid and small bowel. None of these was disturbed. The diaphragm, and the region of the kidneys, gall bladder, liver, and adrenals were free from metastatic growths. The left tube, left ovary and uterus appeared normal; the site of the

right ovary was well healed and free from recurrences. The outstanding observation was that all of the metastatic growths seemed to be superficially implanted. However, only those readily accessible were removed. Recovery was uneventful.

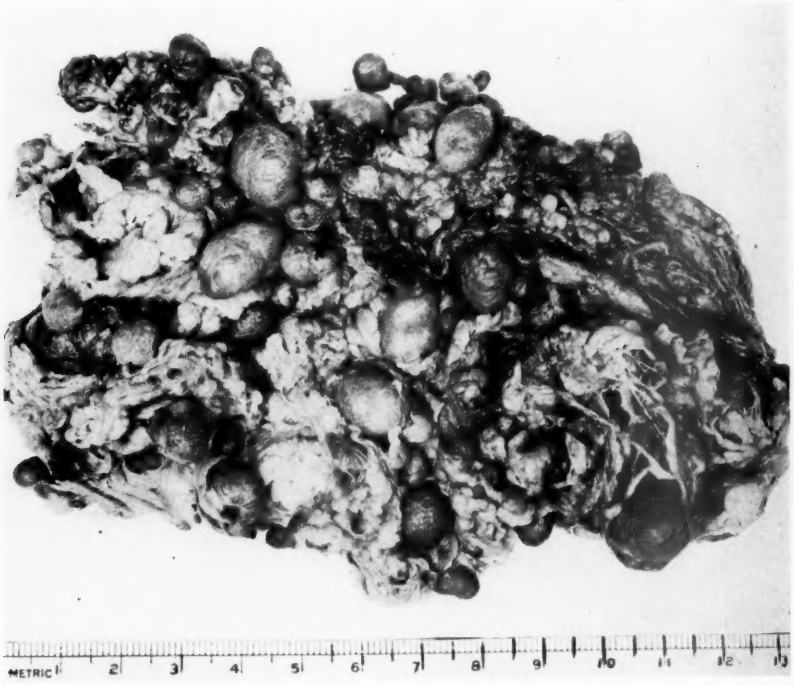

Fig. 6.

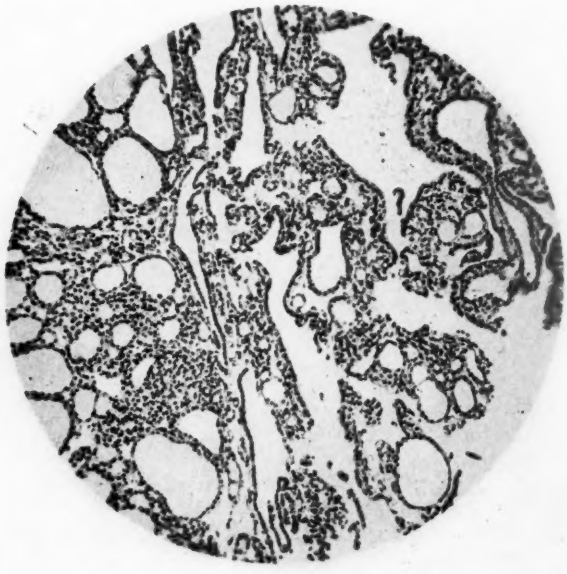

Fig. 7.

Microscopic study of the omental implants revealed an entirely different picture. Hyperplastic changes with villous proliferation and infolding of the lining of follicles were more common, but mitotic figures were strikingly absent (Fig. 7). Mature follicles were distinctly larger, with a readily recognizable increase in Langendorff cells. In many follicles the cellular lining had become flattened to the point of compression of nuclei. The supporting stroma had increased considerably and extrafollicular colloid was hard to find. Hyperplastic areas, as before, were poor in colloid. The general picture was that of a well-organized thyroid struma with moderate hyperplasia.

On March 31, 1939, a bone survey was made and no metastases were found. On April 18 the basal metabolic rate had dropped to plus 4.0 per cent. By August, 1939, all symptoms of hyperthyroidism had disappeared, the basal metabolic rate now being plus 0.9 per cent, weight 122.5 pounds, pulse 72, blood pressure 107/88. The exophthalmus had markedly decreased. The abdomen was soft, and masses could not be palpated. A recent bone survey showed no visible metastases, and the basal metabolic rate has remained at plus 0.9 per cent.

Because of lack of facilities, iodine determinations were not made until after the tissues had been in Kaiserling's solution for from eight to twenty months. Since alcohol and formalin were used in the process of preparation, it is possible that certain protein-bound fractions of iodine were disturbed. However, as far as is known, *total* iodine contents are less affected and reasonably accurate information can still be obtained. Since different methods of determination may yield different results, tissue was sent to two different investigators.* Each received two metastases and one piece of the original tumor tissue. That sent to W. W. Hilty contained less colloid than that sent to A. L. Chaney. The total iodine levels expressed in milligrams per gram of tissue tested was as follows:

	HILTY		CHANEY	
Original tumor	1.055	0.982	0.085	
Metastatic tumors	1.650	0.743	0.086	0.021

Hilty's results correspond to those encountered in early hyperplasia of mildly colloid goiters. Those reported by Chaney would seem without significance were it not that he states in a personal communication that findings of 0.08 mg. per gram approached normal thyroid according to the method employed by him. The interpretation of iodine determinations therefore seems to depend upon standards established for a given method.

The total iodine content of the thyroid gland varies according to hyperplastic activities. According to Marine and Lenhart, morphologic changes parallel iodine content. Expressed in milligrams per gram of dried thyroid tested, they range as follows:

Normal state	2.17 mg.	or 0.22%
Early hyperplasia	0.88 mg.	0.09%
Moderate hyperplasia	0.71 mg.	0.07%
Marked hyperplasia	0.32 mg.	0.03%
Colloid state	2.00 mg.	0.20%

It is pointed out that the thyroid gland may go through these various phases many times during the life of an individual without deviating from this ratio. It is not known that ovarian thyroid acts similarly. Most ovarian strumas are in an arrested state of colloid storage, frequently with no, or only traces of, demonstrable iodine. Smaller

*I am greatly indebted to W. W. Hilty, Control Chemist of Eli Lilly and Company and to A. L. Chaney, Chemist of the Los Angeles County General Hospital, for the determinations of iodine levels. Hilty and Wilson described their own method in Industrial and Engineering Chemistry **11**: 637, 1939. Their method has been extensively used in the assay of defatted and dessicated thyroid. Chaney used a modification of the method of Matthews and Curtis, which digests the tissues without dessication in chromic and sulphuric acid.

tumors still in an active state of growth have not been tested for iodine and hence no criterion is available. It is reasonable to assume that large colloid goiters of the ovary represent very low functional states and hence iodine storage may have dropped to insignificant levels. As matters stand, iodine levels of ovarian strumas not only vary considerably but do not parallel morphologic changes. Of the iodine determinations reported below, none fitted the morphology described on the basis of thyroid standards:

Neu, 1911		0.02%	or 0.2 mg.
King and Norris, 1930	I	0.11	1.1
	II	0.13	1.3
Plaut, 1931 to 1933	I	0.67	6.7
	II	0.02	0.2
Masson and Mueller, 1933	I	0.10	1.0
	III	0.13	1.3
	IV	0.01	0.1

Wynn, McCarthy and McClendon, using different standards, report 0.02 per cent for a colloid tumor and 0.009 per cent for its ischial metastasis with a reversed ratio for thyroid hormone iodine (0.005 per cent and 0.028 per cent). For the sake of comparison, their figures have been changed from micrograms to percentages. Our own experience with the results of two experienced investigators makes us doubt the constancy of iodine throughout a given tumor. This, together with technical differences, must seriously influence results. So far, iodine studies of ovarian strumas have not materially added to the knowledge of their functional activity. Such studies, however, have shown that ovarian strumas store iodine, though not in the same ratio to morphologic changes as does the thyroid gland. The functional importance of these tumors, on the basis of iodine determinations alone, cannot be great. However, clinical evidence permits the conclusion that in isolated instances ovarian strumas may produce thyrotoxicosis.

GROWTH CHARACTERISTICS

Most strumas of the ovary are benign tumors with orderly growth habits. It is not known when they begin nor how long they grow. They are decidedly more common after the age of maturity, and to my knowledge, are not encountered in early childhood. When part of an ordinary teratoma, they may not be encapsulated but may freely intermingle with other tissue. When they are encountered as a so-called pure struma they always have a capsule formed by mesoderm derivatives. Perforation of the capsule by direct invasion is extremely rare. Attempts to classify ovarian thyroids according to morphologic appearance into macrofollicular, microfollicular, and hyperplastic groups have been made by several investigators. There is, however, evidence that the morphologic structure of the ovarian tumor does not necessarily indicate its functional activity and hence no particular help is derived from such classifications. Besides, large tumors do not necessarily present a uniform morphologic picture but may show various stages of cellular activity in different regions of the tumor. In general, their tendency is to develop into a colloid goiter rather than to maintain hyperplastic activities, and it is granted that when the latter is present different degrees of hyperplastic action may occur within the same tumor. As a rule, the severer types of hyperplasia are rarely encountered.

Although there are no reliable figures, about 5 to 6 per cent of these tumors may be expected to assume metastatic growth habits. There are now nine such cases on record, including the one reported here (Table I). Metastases from an ovarian thyroid are not necessarily fatal. Only about one-half of the patients reported died as a result of metastatic invasion. Contrary to the behavior of metastatic neoplasms of the thyroid gland, metastases from an ovarian thyroid are ordinarily con-

TABLE I

AUTHOR	YEAR	DIED AFTER OPERATION	ASCITES	METASTASIS	REMARKS
K. Kretschmar	1904	21 mo.	+	Not stated	Many dense adhesions in abdomen. Died with ascites.
F. Proescher and J. A. Roddy	1910	2 yr.	+	+	Carcinomatous change of struma present at time of operation.
F. Proescher and J. A. Roddy	1910	1 yr.	+	+	Recurrence in 5 months in liver and mesentery. Mesenteric nodule same as parent tumor.
M. Morgen	1924	18½ yr.	++	+	Died from intercurrent disease at 74. Many small peritoneal implants at operation and at autopsy. (Benign strumosis.)
G. Werth	1928	Alive six months	+	+	Metastases restricted to pelvic organs. Radiated—discharged as cured. No further information.
P. F. Shapiro	1930	Autopsy diagnosis	+	+	Died from uremia. Strumosis considered benign; probably present for a long time. (Benign strumosis.)
L. D. Eesland	1936	Unknown	?	+	Original article not available. Metastases to cranium.
Wynn, McCarthy and McClendon	1940	Alive 3 yr.	0	+	Bone metastasis (ischium) 1 yr. postoperative—removed. Primary tumor had area of malignancy.
L. A. Emge	1940	Alive 2 yr.	0	+	Omental and mesenteric metastases. Hyperthyroidism. Second operation: No particular increase in size of metastases. Disappearance of toxic symptoms after removal of omental metastases. Probably benign strumosis.

fined to the abdominal viscera and are more often superficial than invasive. Omental metastases have been reported. Bone metastases, which is more in line with the behavior of malignant thyroid tumors, have been reported twice. In most instances, ascites has accompanied metastatic growth, although Wynn and others, as well as ourselves, found none. Metastases, if not invasive, seem to have a growth limit and may regress, as reported by Morgen. In the case reported here, the increase in size in omental metastases was comparatively small after one year, as far as could be determined at the second operation. At times, a parent tumor may appear morphologically benign and still produce malignant metastases. However, small areas of malignant degeneration may be easily overlooked.

The presence of metastases may or may not disturb the health of the host. The patient observed by us, though still harboring a large amount of aberrant tissue, continues in good health. Two bone surveys have failed to demonstrate metastatic invasion, which serves as a fair criterion for the relatively benign character of the growth. Patients may live many years with multiple aberrant thyroids, as demonstrated by Morgen's patient, who died at 74, eighteen and one-half years after operation, with known metastases still present at autopsy. Whether irradiation can arrest the growth of metastatic strumosis is conjectural. Werth described multiple metastases confined to the pelvis which were irradiated after removal of the genital organs. Unfortunately, the ultimate outcome of this case is not known. Metastatic growth, when it assumes malignant tendencies, usually kills quickly.

Table I sets forth some of the important observations described in conjunction with the 9 metastatic ovarian strumas now recorded.

The fact that some ovarian strumas can produce malignant metastases makes it imperative that careful study of the abdominal cavity be done at the time of operation and that bone surveys be made at least once a year thereafter. As described here, it is possible at times to remove safely part of the metastases, particularly when the condition gives rise to thyrotoxic disturbances, or when bone implantation has occurred, as described by Wynn and others. Ascites accompanies many of these tumors and, in itself, is not indicative of malignancy.

SUMMARY

1. It is estimated that from 5 to 6 per cent of ovarian strumas produce thyrotoxicosis.

2. Morphologic changes do not necessarily parallel the degree of toxicosis.

3. The majority of ovarian strumas store very little iodine.

4. The degree of iodine storage does not parallel morphologic changes.

5. From 5 to 6 per cent of these tumors produce metastases, half of which kill by malignant invasion.

6. Metastases are usually confined to the abdomen.

REFERENCES

(1) *Anspach, B. M.:* Univ. Penna. Med. Bull. **16:** 337, 1904. (2) *Aschkanasy, K.:* Monatschr. f. Geburtsh. u. Gynäk. **103:** 203, 1936. (3) *Boettlin, E.:* Virchow's

Arch. **115:** 493, 1889. (4) *Cantor, P. J., and Kogut, B.:* Am. J. Cancer **28:** 760, 1936. (5) *Frank, R. T.:* Am. J. Obst. **60:** 433, 1909. (6) *Frankel, J. M., and Lederer, M.:* Am. J. Obst. & Gynec. **16:** 367, 1928. (7) *King, E. S. J., and Norris, J. H.:* J. Coll. Surg. Australas. **3:** 373, 1930-1. (8) *Kleine, H. O.:* Arch. f. Gynäk. **158:** 62, 1934. (9) *Koucky, J. D.:* Ann. Surg. **81:** 821, 1925. (10) *Kovacs, F.:* Arch. f. Gynäk. **122:** 766, 1924. (11) *Lyday, R. O.:* Am. J. Surg. **25:** 89, 1934. (12) *Marine, D., and Lenhart, C. H.:* Arch. Int. Med. **3:** 66, 1909; **4:** 440, 1909. (13) *Masson, J. C., and Mueller, S. C.:* Surg. Gynec. Obst. **56:** 931, 1933. (14) *Moench, G. L.:* Ibid. **49:** 150, 1929. (15) *Morgen, M.:* Virchow's Arch. **249:** 217, 1924. (16) *Neu, M.:* Monatschr. f. Geburtsh. u. Gynäk. **34:** 251, 1911. (17) *Neumann, H. O.:* Arch. f. Gynäk. **163:** 600, 1937. (18) *Norris, C. C.:* Am. J. Obst. **60:** 985, 1909. (19) *Nicholson, G. W.:* Guy's Hospital Reports **87:** 391, 1937. (20) *Outerbridge, G. W.:* Am. J. Obst. **68:** 1032, 1913. (21) *Plaut, A.:* Klin. Wchnschr. **10:** 1803, 1931; Am. J. Obst. & Gynec. **25:** 351, 1933. (22) *Proescher, F., and Roddy, J. A.:* Am. J. Obst. **61:** 619, 1910. (23) *Ries, E.:* Surg. Gynec. Obst. **18:** 262, 1914. (24) *Rohdenburg, G. L.:* J. Lab. & Clin. Med. **12:** 211, 1926. (25) *Shapiro, P. F.:* Ann. Surg. **92:** 1031, 1930. (26) *Simpson, W. M.:* Surg. Gynec. Obst. **42:** 489, 1926. (27) *Strong, L. W.:* Am. J. Obst. **70:** 410, 1914. (28) *Werth, G.:* Zentralbl. f. Gynäk. **52:** 2944, 1928. (29) *Wood, F. C.:* Proc. N. Y. Path. Soc., N. S. **9:** 51, 1909. (30) *Wynn, H. M. N., McCarthy, J. S., and McClendon, J. F.:* Am. J. Obst. & Gynec. **39:** 263, 1940.

DISCUSSION

DR. JOHN MASON HUNDLEY, JR., Baltimore, Md.—During the past year a patient with struma ovarii, showing signs of thyrotoxicosis, has been observed in the Gynecological Department of the University of Maryland by Dr. Edward P. Smith, who has kindly given me permission to make this report.

H. H., 41 years of age, single, was admitted to the Mercy Hospital, May 9, 1939. She complained of a rapid pulse, heart irregularity, shortness of breath on exertion, and headaches, these symptoms having been present for the past five months. The past history was essentially negative. The menstrual history revealed nothing abnormal, the periods having always been regular, occurring every twenty-eight days, lasting two days, and being rather scant. During the past year, the patient has felt tired most of the time and has lost eight pounds.

She was a slender, nervous woman whose weight was 112 pounds. The eyes showed no signs suggestive of exophthalmic goiter, and the thyroid gland was not palpable. A slight pleuropericardial friction rub near the base of the sternum and a moderate degree of cardiac hypertrophy were present. The blood pressure was 139/72, pulse 110 with normal rhythm. An area of dullness was noted in the suprapubic region, which extended upward nearly midway to the umbilicus. There was a fine tremor of the extended fingers. A pelvic examination did not seem indicated. The impression at this time was moderate cardiac hypertrophy with borderline decompensation. Hyperthyroidism, however, had to be ruled out.

The basal metabolic rate in six tests varied from a plus 22 to a plus 42. The electrocardiograms showed only a tachycardia. The teleoroentgenogram of the thorax showed nothing abnormal, no substernal thyroid being observed. Blood chemistry, blood counts, and serologic tests were normal, as were the examinations of the urine and stools. The sedimentation rate was 20 mm. in one hour.

A diagnosis of hyperthyroidism was then made, and the patient was placed on Lugol's solution, minims v, t.i.d., sedatives, and "thyroid" diet. The pulse improved with bed rest but the basal rate remained elevated. On June 2, twenty-three days after admission, a subtotal thyroidectomy was done by Dr. Daniel Pessagna, and the gland showed definite evidence of hyperplasia. The pathologic report is as follows: "In the sections from the thyroid, the acini were rather uniform in size. They were lined by cuboidal and flattened epithelial cells and contained chromophile colloid. A few small scattered areas of hyperplasia were noted. An occasional spur was seen. There were many nodules of lymphoid tissue scattered through the sections. The tissue was somewhat lobulated. *Diagnosis:* Hyperplastic goiter, involution stage."

The patient had an uneventful convalescence and was discharged on June 15, 1939, but her progress at home was not encouraging. She was constantly confined

to bed due to weakness and exhaustion on the slightest exertion, and the palpitation and dyspnea became gradually more marked.

In September, 1939, it was noticed that her abdomen was increasing in size, and she began to have frequency of urination. At this time, the pulse rate was 130 and emotionally she was much more unstable than prior to operation. The fine tremor of the fingers and the sweating of her palms became increasingly noticeable. In spite of these signs of persistent thyroid activity, the patient gained 25 pounds. For the first two months after leaving the hospital, she received Lugol's solution, minims iii, but this was then discontinued.

On Nov. 15, 1939, the patient was re-admitted to the hospital. The most noteworthy change in the physical examination was increased abdominal enlargement and more extensive suprapubic dullness, this extending upward 7 cm. On gynecologic examination an indefinite, slightly tender mass was found in the right lower abdomen. Rectal examination revealed a large, round, smooth, slightly tender mass in the right adnexal region, the uterus being crowded into the left pelvis. A diagnosis of right ovarian cyst was made.

Basal metabolic rates were again determined and were found to be consistently plus 30. Routine laboratory work was normal. An iodine tolerance test was done which showed an extremely high fasting level, namely 48. The patient was treated as a case of hyperthyroidism but with no avail, the pulse remaining elevated.

As the patient continued to show signs of thyrotoxicosis after the subtotal thyroidectomy, it was felt that sufficient aberrant thyroid tissue might be present in the ovarian cyst and thus be the focus of the continued toxic symptoms. On Nov. 29, 1939, a laparotomy was performed by Dr. Edward P. Smith, and there was found a right dermoid cyst, small multiple myomas, and cystic degeneration of the left ovary. No evidence of malignancy or metastatic masses was observed. A bilateral salpingo-oophorectomy and a supravaginal hysterectomy were done. Immediately after operation, the pulse became quite rapid, reaching 130, but fell on the following day to 100. The convalescence was uneventful, the thyrotoxic symptoms quickly subsided, and the pulse rate soon dropped to 75. Eight days following the operation the basal metabolic rate was minus 6.

Pathologic Report.—"The right ovary measures 13.9 by 10.4 by 12.7 cm. A portion of the ovary is replaced by a cystic mass 3.5 cm. in diameter; the remaining portion is replaced by a solid tumor, 9 by 5 by 5 cm. On section, the cystic portion is found to contain hair and ceruminous material, while the wall is smooth-lined and moderate in thickness. This portion is typical of a dermoid cyst. The solid portion of the tumor on section is found to be divided up into lobules by trabeculae. The inner trabecular portions seem to be somewhat gelatinous in appearance, yet feel rather firm. Interspersed in the gelatinous portions are small areas of yellowish brown tissue. This solid area is suggestive of thyroid tissue. The myomatous uterus, tubes, and left ovary show nothing noteworthy."

Microscopic Description.—"In the sections of thyroid tissue from the ovary, there is marked variation in the size of the acini. Some are quite small, others are widely dilated. The lining cells vary from columnar to a flattened, scale-like type. Hyperplasia in areas is fairly well marked. Remnants of papillae and spurs are noted. Colloid is chromophile in character. There are a few lymphoid nodules present. Diagnosis: Hyperplastic goiter, involution stage."

CARCINOMA OF THE OVARY*

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THIS paper is an analysis of 149 cases of primary carcinoma of the ovary occurring among a total of 855 patients with ovarian tumors, excluding retention cysts, treated in the Free Hospital for Women and its private ward by the various members of the staff from 1906 to 1938. It includes papillary, adenomatous, and medullary carcinomas. The classification and nomenclature of ovarian tumors are not standardized. We have decided to use Schiller's designation of adenopapillary carcinoma for these cystic types. They are subdivided into serous and pseudomucinous adenopapillary carcinoma, which appear to progress somewhat differently. Each of these is divided into those which show a gross semisolid structure of adenomatous tissue in part or whole and predominantly cystic ones. Finally, there are the medullary tumors.

MATERIAL

The age groups at which the tumor occurred are as follows:

20-30	4
30-40	17
40-50	46
50-60	47
60-70	28
70-	7
	149

The youngest was 26, but there are reports in the literature of still younger ones, Lynch having 1 of 16 years, for instance. The oldest was 86. The average age was 49. Sixty-one per cent occurred between the ages of 40 and 60. Therefore an ovarian tumor removed at any age must be considered as possibly carcinomatous.

Twenty-eight (19 per cent) were unmarried, which is near Lynch's 17 per cent and lower than in most reports. Eighty-one (66 per cent) of the 121 married women had from 1 to 10 living children, and 15 (12 per cent) had miscarriages only. Therefore, only 25 (22 per cent) were completely sterile. The first figure corresponds with Lynch's report that two-thirds of the married women had borne children, but 31 per cent of his patients had never been pregnant, as against our 22 per cent. It does, however, substantiate his argument that there may be an etiologic factor, in that women who develop cancer of the ovary show a reduced fertility.

The menstrual history of these patients is as follows:

Still menstruating:			
Normal	49		
Menorrhagia	7		
Metrorrhagia	7		
		63	
Menopause:			
Natural	79		
Operative	4		
Radium	2		
X-ray	1		
		86	149
Flow after menopause	6		

*Read at the Sixty-fifth Annual Meeting of the American Gynecological Society, Seigniory Clube, Que., June 17 to 19, 1940.

These figures show no well-defined connection between this type of ovarian carcinoma and menstrual abnormalities, certainly nothing of diagnostic significance. Any flow after the menopause should make one think of an endometrial metastasis or a primary tumor.

The operations done on these patients were as follows:

Hysterectomy, bilateral salpingo-oophorectomy	105
Hysterectomy, unilateral salpingo-oophorectomy	6
Bilateral salpingo-oophorectomy	7
Unilateral salpingo-oophorectomy	23
Exploratory	8
	149

We believe that the uterus and both tubes and ovaries should be removed whenever possible, because bilateral growths occur so often and metastases are found frequently in the back of the uterus. It is often difficult and possibly useless to attempt this, however, when the pelvis is filled with the growth and adherent omentum and intestine. The tumor should be removed intact, if possible, and tapping to decrease its size for easier removal should be reserved for elderly patients and poor risks.

We believe that when an operation for cancer of the ovary is done it would be wise to remove the omentum, regardless of whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrences later.

Sixteen patients had had previous treatment for pelvic disease. A patient of 47 years had had her uterus removed six years previously, for reasons unknown to us, and came in with generalized carcinoma, involving both ovaries. The ovarian tumors could have arisen since the operation. A 68-year-old patient had had some pelvic operation five years before, and we did an exploratory operation only because of the advanced disease. Another of 49 years of age had had one ovary removed five years before, and we found general metastases and removed the tumor of the other ovary. Another of 65 years had had an exploratory operation done at the age of 63. We could remove only one tumor because the disease involved the whole pelvis and abdomen. The same was true of another patient, aged 54 years, who had had an exploratory operation three years before. A 51-year-old woman had had an appendectomy six years previously, at which time a small cyst of the ovary was noted but not removed. We removed her uterus and both ovaries for a unilateral 8-inch cystic tumor, and she is well five and one-half years after operation. One patient, aged 37 years, had had a left oophorectomy nine years before, and we removed the uterus and right ovary for a 3-inch cystic tumor; she is still well five years after operation. There was probably no connection between the two.

A 45-year-old patient had had the menopause induced by x-ray at age of 35; she had had a left oophorectomy for a cyst said to have been malignant at age of 42, and we removed the uterus and right ovary for a 4-inch cystic tumor which ruptured during the operation. She had postoperative x-ray treatment and is well five years following operation. It would have been reasonable to have removed both ovaries and the uterus at 42, since she had already had the menopause.

A patient, aged 45 years, had had her left ovary removed eight years earlier and her uterus five years before we saw her. We excised the other ovary for an 8-inch cystic tumor, gave her x-ray treatment, and she is well 3½ years following operation. One patient, aged 42, had been operated upon for a cystic ovary four years previously, leaving a sinus. We were able to remove the uterus and other ovary, which were very adherent, gave her x-ray treatment, and she is apparently well two and one-half years after operation.

A woman, aged 55 years, had been treated with radium for flowing five years earlier, which induced the menopause. We found a unilateral semisolid tumor, re-

moved the uterus and ovaries, gave her x-ray treatment, and she died in nine months. Another patient, aged 62, had had a cyst removed a year previous to our hysterectomy and unilateral oophorectomy for a 6-inch cyst which was very adherent, and she died of recurrence in one year. If she had had a radical operation the first time she might have been saved.

A 35-year-old patient had had an ovarian cyst removed eleven years before we did a hysterectomy and a right salpingo-oophorectomy for a cystic tumor. She is living nine years after operation with disease. One patient, aged 63, had had a hysterectomy and unilateral oophorectomy twenty-six years earlier, and we removed the other ovary for an adherent cystic tumor which ruptured, and she died in three years of heart disease, apparently cured of her cancer. Another patient, aged 69, had been treated with x-ray a year before, and we found bilateral cystic tumors. She appears to be well two and one-half years later. It does not seem to be generally realized that pelvic tumors arising after the menopause are nearly always ovarian and not fibroids of the uterus. So far as we could determine, this woman had been treated with x-ray on a diagnosis of fibroid. Finally, a patient, aged 49 years, was treated in our hospital with 1,200 mg. hr. of radium for menorrhagia two years before a tumor in the pelvis was felt. It was doubtless present at the previous examination but too small to be found. She not only had a semisolid ovarian tumor 5 inches in diameter, but early carcinoma of the endometrium and advanced carcinoma of the cecum, all different tumors. The endometrium at the radium treatment showed hyperplasia, but it is, of course, possible that there were areas of carcinoma which were not sectioned. She had no flowing after the radium treatment. We did a hysterectomy, bilateral salpingo-oophorectomy, and excision of the ascending colon. She received postoperative x-ray treatment and lived three years, dying of metastases in the upper abdomen and chest wall on the right, probably from the intestinal cancer.

The number of cases in the various pathologic divisions of these tumors are as follows:

Serous adenopapillary carcinoma, semisolid	44
Serous adenopapillary carcinoma, cystic	70
Pseudomucinous adenopapillary carcinoma, semisolid	10
Pseudomucinous adenopapillary carcinoma, cystic	18
Medullary carcinoma	6
Pseudomyxoma peritonei	1

The differentiation between serous and pseudomucinous is usually definite, but a few cases contained both, so the predominating type was chosen in such instances. The designation semisolid contains a large personal equation, and we have put in that class the tumors that had gross areas of semisolid tissue which showed an adenomatous appearance microscopically. The medullary carcinomas are solid tumors. In previous years many had been called solid carcinomas which, in light of more recent knowledge, proved to be granulosa cell tumors and were excluded from this series after I reviewed the slides. There is a difference of opinion as to whether or not pseudomyxoma peritonei is a malignant disease, but since it is progressive we have included our 1 case.

At operation the tumors were designated as unilateral or bilateral in all but 3 instances where the disease was so advanced that it could not be determined. The tabulation is as follows:

	UNILATERAL	BILATERAL
Serous	63 (53%)	55 (47%)
Pseudomucinous	25 (82%)	3 (18%)

Seventy-one cases (47 per cent) had enough ascites for it to be noted in the operative record. In 121 instances (80 per cent), the tumors were described as

being adherent to other organs. The tumor was ruptured during removal in 34 (22 per cent) patients because it was adherent or necrotic in places. Metastases were general throughout the abdomen in 31 (20 per cent). They were described as confined to the pelvis in 25 (16 per cent), but in 16 of these the pelvis was practically solidly occupied by tumor masses. Adding these last two estimates, there were 36 per cent in which the extent of the disease should prevent a cure. Certainly earlier diagnosis is essential.

We have attempted to grade the degree of malignancy by considering the amount of differentiation and number of mitotic figures shown by microscopic examination. The tumors vary so much in their histologic appearance that it is difficult to grade them. The patterns and epithelial cells vary from a very simple papillary growth with low cells and not much invasion to semisolid adenomatous tumors with metaplasia, resembling carcinoma of the endometrium. Our result is as follows, Grade 1 being the least malignant:

Grade 1	49	32%
Grade 2	59	40%
Grade 3	41	28%

When graded in the subdivisions we obtain this result:

Grade	1	2	3
Serous adenopapillary carcinoma	36 (32%)	45 (39%)	33 (29%)
Pseudomucinous adenopapillary carcinoma	12 (43%)	12 (43%)	4 (16%)
Medullary carcinoma	0	1	5
Pseudomyxoma peritonei	1	0	0

This is further evidence that the serous are somewhat more malignant than the pseudomucinous tumors, since a larger proportion of them fall in Grades 2 and 3.

There were 6 medullary carcinomas, 2 of which were bilateral. They were all advanced, very adherent, and so friable that the tumors tore and were removed in pieces. In 2 cases an exploratory operation only could be done. One had a right salpingo-oophorectomy, 1 a bilateral salpingo-oophorectomy, and in 2 the uterus and both tubes and ovaries were removed. Five were graded at 3 and 1 at 2 for malignancy. There was 1 postoperative death and the others died in less than fifteen months. The longest survivor received 7,000 roentgens of x-ray after an exploratory operation. Another patient lived a year with the aid of a colostomy done for partial obstruction at the removal of her tubes and ovaries, the uterus having been removed three years previously elsewhere. These 6 patients were 41, 54, 57, 60, 64, and 78 years of age. Five were past the menopause, with no bleeding or discharge, and 1 was menstruating normally.

It would seem that these are very insidious tumors, in that they become adherent and grow without symptoms until it is too late for cure. The patients complained of discomfort in the lower abdomen only, except for 2 who had noticed some swelling.

The patient with pseudomyxoma peritonei was 34 years old in 1894 when she had a bilateral salpingo-oophorectomy for this bilateral tumor. At that time there were large masses of gelatinous material throughout the abdomen. In 1907, thirteen years later, she was again operated upon and the uterus and various masses of tissue were removed. The tumor was in all parts of the abdomen. She died two years later, fifteen years after the original operation. These are relatively benign but persistent tumors and may or may not be classed as true malignant ones.

There were 6 cases in which metastases occurred to the endometrium.

Patient 18-127, aged 33, white, married twelve years, entered the hospital May 23, 1911. She had had two children and one miscarriage. Her last pregnancy was eight years ago. Catamenia was normal, every twenty-eight days, lasting five days. Operation: Right salpingo-oophorectomy. Supravaginal hysterectomy. Cyst ruptured during removal. Pathology: Unilateral, adenopapillary carcinoma, right ovary, 12 inches in diameter. Adenocarcinoma, endometrium metastatic. The whole endometrium was involved. Tube negative. Untraced.

Patient 31-197, aged 36 years, white, married twelve years, entered the hospital May 1, 1919. There had been no pregnancies. Catamenia was menorrhagic for one year. Operation: bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, left ovary, 6 inches in diameter. Normal right ovary. Adenocarcinoma, endometrium metastatic, small area at fundus. Tubes normal. Well, twenty years.

Patient 27-51, aged 40 years, white, married fourteen years, entered the hospital Nov. 23, 1916. She had had six children. Her last pregnancy occurred four years ago. Catamenia was regular every twenty-eight days, lasting ten days, except for a period of six months when she had menorrhagia. Operation: Bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, right ovary, 5 inches in diameter. Normal left ovary. Adenocarcinoma, endometrium metastatic, small area in fundus. Tubes normal. Well, seven years.

Patient 2243, aged 43 years, white, married six years, entered the hospital May 17, 1928. There had been no pregnancies. The catamenia was normal and regular every twenty-eight days, lasting seven days. Operation: Bilateral salpingo-oophorectomy. Supravaginal hysterectomy. Cyst adherent. Pathology: Adenopapillary carcinoma, left ovary, 6 inches in diameter. Metastasis to right ovary. Endometrioma, right ovary. Adenocarcinoma, endometrium metastatic, small area in fundus. Metastatic carcinoma in lumens of both tubes. Died eight months after operation.

Patient 15-296, aged 45 years, white, married fifteen years, entered the hospital March 25, 1909. She had had one miscarriage fifteen years ago. Catamenia had ceased six months before entrance into hospital. There was no discharge. Operation: Bilateral salpingo-oophorectomy. Complete hysterectomy. Cyst adherent, ruptured during removal. Pathology: Adenopapillary carcinoma, right ovary, 10 inches in diameter. Normal left ovary. Adenocarcinoma of endometrium, metastatic, whole surface involved. Metastases in right tube and cervix. Untraced.

Patient 23029, aged 43 years, white, married fourteen years, entered the hospital on Jan. 15, 1933. She had had one miscarriage. Catamenia was normal and regular every twenty-eight days, lasting three days. Operation: Supravaginal hysterectomy. Bilateral salpingo-oophorectomy. Appendectomy. Pathology: Bilateral adenopapillary carcinoma of ovaries. Adenocarcinoma of endometrium, area 1.5 cm. in diameter, on left wall. X-ray treatment, 4,800 r. postoperative. Died five years after operation for metastasis in lung.

That metastases to the endometrium occur is recognized by various pathologists, but it is also acknowledged that it is often difficult to prove whether the tumor was primary in the ovary or uterus. Sternberg, in his section on ovarian tumors in Halban and Seitz, quotes Pfannenstiel, Arzt, Lessing and Schanta as believing that ovarian tumors may metastasize to the endometrium and Pfannenstiel says it is more common than the reverse. Boyd also agrees that it may occur. According to our figures, 6 ovarian tumors out of 149 metastasized to the endometrium, that is 4 per cent, while 12 out of 305 of endometrial cancers showed metastases in the ovary, that is 4 per cent.

Metastases from the ovary to the endometrium may occur by extension through lymphatics and veins, by direct growth through the uterine wall and by extension through the tube or implantation of free pieces of tissue flowing through the tube into the uterine cavity.

Sampson has described 12 instances of metastases in the lumen of the tube, 2 of our 6 cases under discussion show the same, and it is reasonable to suppose that the endometrial growth may have arisen from them. The ages of our 6 patients were 33, 36, 40, 43, 43, and 45 years. Cancer of the endometrium is uncommon under 45. This is another point in favor of the ovary-to-endometrium course in 5 of the above instances. Furthermore, in 4 of our cases the endometrial growth was small and at the top of the uterine cavity. Since such metastases occur, this is an added reason for doing a hysterectomy if possible. Forty-four (29 per cent) patients had other tumors. Fibromyomas of the uterus were present in 30.

Endometriosis was associated with the carcinoma in 10 instances. It is reasonable to suppose that this disease may be the source of carcinoma of the ovary, but it is difficult to prove the relation in any specific case, and we were not able to in these.

Benign serous cystadenomas occurred in the other ovary in 2 patients, a benign pseudomucinous cyst in 1, a cystadenofibroma in 1, and sarcoma in 1.

Carcinoma of the cecum was present as a primary tumor in 2 cases and carcinoma of the endometrium in 5.

Therefore, one should survey the field for other tumors before deciding on the method of procedure, and a curettage should be done as a first step; for with these 5 primary tumors of the endometrium and the 6 metastatic ones, there are 11 cases with involvement there.

There were 37 patients with semisolid serous adenopapillary carcinoma operated upon five or more years ago, and only one is living and well.

Untraced	4
Postoperative death	2
Dead	
0-1 year	12
1-2 years	10
2-3 years	4
3-4 years	2
8 years	1
28 years	1
Living 6½ years	1

Twenty-two (71 per cent) out of 31 that survived operation died before the end of the second year after operation. The patient that lived 8 years had a hysterectomy and bilateral salpingo-oophorectomy for a unilateral Grade 2 tumor and died of heart disease. The patient that lived twenty-eight years had a left salpingo-oophorectomy for a unilateral Grade 1 growth at the age of 47, and a year later the other ovary was removed for a serous cystadenoma. She died twenty-seven years later of heart disease; an autopsy showed no sign of cancer. The patient who was living and well after six and one-half years had a hysterectomy and bilateral salpingo-oophorectomy for a unilateral Grade 2 tumor and received 6,400 roentgens of x-ray after operation. This is certainly a discouraging list of cases, since only 3 out of 37 were apparently cured by treatment.

The picture is more cheering when we consider the cystic adenopapillary carcinomas, of which 53 were treated five or more years ago. The statistics are as follows:

Untraced	6		
Postoperative death	2	LIVING, WELL	
DEAD		5-6 years	7
0-1 year	10	7-8 years	1
1-2 years	5	8-9 years	2
2-3 years	3	13-20 years	6

3-4 years	2	LIVING, WITH DISEASE	
4-5 years	3	5 years	1
8 years	1	9 years	1
12 years	1	15 years	1
14 years	1		

Fifteen (28 per cent) out of the 51 that survived operation died before the end of the second year. Of those dead, the eight-year survivor died of cancer. The original operation showed a primary adenocarcinoma of the endometrium as well as the unilateral ovarian tumor in a woman 45 years of age. A complete hysterectomy and bilateral salpingo-oophorectomy were done. Recurrences were excised from the abdominal wall three and four years after the first operation but the disease continued. The twelve-year survivor died of diabetes and the 14-year one of heart disease; both apparently were cured of their cancer. There are 16 living and apparently well. Thirteen had a hysterectomy and bilateral salpingo-oophorectomy done. Two had a hysterectomy and right salpingo-oophorectomy done, the other ovary having been removed three and nine years before. We could not obtain the diagnosis on the first operations. The last patient is living and well thirteen years after a left salpingo-oophorectomy done at the age of 71 years. The tumor which ruptured during the operation was 10 inches in diameter, and the other ovary, which was left in, has apparently caused no trouble. Eight had bilateral tumors and 8 unilateral. The tumor was ruptured in 4 instances during removal. An eight-year survivor had definite peritoneal metastases, another had metastases in the omentum, which was removed, and a five-and-one-half-year apparently well patient had an everting papillary growth. These patients had tumors of low malignancy, 12 being Grade 1 and 4 Grade 2. Five of them were treated with x-ray after operation.

There are three living with the disease five, nine, and fifteen years after operation. The first had her uterus, tubes, and ovaries removed for a unilateral tumor which ruptured during the operation. She was treated with x-ray but received only 2,800 roentgens. The second patient had had her left ovary removed eleven years before for a malignant papillary cystadenoma. We did a hysterectomy and right salpingo-oophorectomy for a Grade 1 cyst, 8 inches in diameter, very adherent, and removed a metastasis in the abdominal wall. She has a mass in her pelvis which is being treated with x-ray. The last one, now at 15 years, had her uterus, tubes, and ovaries removed for bilateral tumors, 4 and 2 inches in diameter, which were adherent. They show a Grade 1 malignancy. She seemed well until six years ago, after which we lost trace of her, but last year she was tapped for ascites at the Brigham Hospital, and 10 quarts of fluid were removed. She received x-ray treatment. Cells removed from the fluid were consistent with carcinoma of the ovary.

Therefore in this series of 53 adenopapillary carcinomas, there are 16 patients alive and well more than five years after operation, 2 who died twelve and fourteen years after treatment, apparently cured of their ovarian tumors, and 3 surviving with disease, a five-year salvage of 39 per cent.

The total number of patients with serous adenopapillary carcinomas treated more than five years ago is 90, and there is a five-year salvage of 25, only 27 per cent.

There were 24 patients with pseudomucinous adenopapillary carcinoma treated more than five years ago.

Untraced	1		
DEAD		LIVING, WELL	
0-1 year	5	5-6 years	1
1-2 years	2	6-7 years	2
2-3 years	1	7-8 years	1
3-4 years	1	13 years	1
4-5 years	2	14 years	1
5-6 years	2	16 years	1
6-7 years	2		
15 years	1		

Of those enumerated as dying more than five years after treatment, 3 died of cancer, 1 was apparently well at six years and then was lost trace of, and 1 died of pernicious anemia at fifteen years. The 7 living are apparently well. There was a five-year salvage of 12 (50 per cent).

These tumors may also be divided into 10 semisolid and 18 cystic for the total number of 28. Of the 12 patients surviving after five years, only 1 had a semisolid tumor; that is, the cystic ones are much less malignant.

To summarize, 114 of these patients with adenopapillary carcinoma were treated more than five years ago and 37 lived five or more years after treatment (32 per cent). The semisolid tumors of both types are much more malignant than the cystic ones and the serous type more so than the pseudomucinous.

The deaths for the 149 cases occurred at the following years:

Postoperative	10
0-1 year	33
1-2 years	26
2-3 years	9
3-4 years	6
4-5 years	5
5-6 years	2
6-7 years	2
8-9 years	2
12-13 years	1
14-15 years	1
15-16 years	2
28 years	1

Sixty-nine (47 per cent) did not survive more than two years.

The five-year end results of treatment as a whole are certainly discouraging. Some patients appear to be well on examination but may have areas which cannot be felt but will develop later, so a ten-year period of observation is necessary, as Lynch suggested. The percentage of five-year salvage varies in different reports from 10 per cent to 35 per cent. Our 32 per cent corresponds very nearly to Lynch's 35 per cent of all the tumors, and our 50 per cent salvage in the pseudomucinous type to Meigs' 50 per cent with the same. The striking fact in our series is that 36 per cent were obviously incurable when seen and Meyer says 55 per cent of his were.

Therefore earlier diagnosis is essential and that can be obtained only by preventive examinations, since these are silent growths for a long time. I have found only one ovarian tumor by that means in my private practice, but it is probable that few gynecologists have a large enough number of patients coming for yearly or semi-yearly examinations to discover many developing tumors of this type. This particular patient of 60 years had a benign serous cystadenoma grow, after a negative examination, to a size of 6 inches in the course of one year without symptoms of any kind. If other similar reports could be obtained the rate of growth could be determined.

Twenty-nine patients have received postoperative x-ray treatment. Sixteen are apparently well from two to six years after treatment, the average being 4.5. One is alive with disease four years from the first

treatment. Twelve had died at from one-half to six years; an average of two years.

The treatment was started usually about three weeks after operation and from 3,200 to 9,100 roentgens were given. We do not treat patients who are emaciated and in very poor general condition, because the gastrointestinal upset and toxemia following the application of x-ray may tip the scales adversely.

Twenty tumors were unilateral and 9 bilateral. They were graded as follows: 14 at Grade 1, 8 at Grade 2, and 7 at Grade 3.

There were evident pelvic metastases in 10, 4 of whom died in five months, ten months, two years, and two and one-fourth years, respectively. Three were Grade 3 and 1 Grade 2. There are 6 apparently well, 1 at two and one-half, 1 at three, 2 at four, 1 at five, and 1 at six years. Five of these were Grade 1 and 1 Grade 2. It would seem that the x-ray had been of benefit in these patients.

Three patients had general abdominal metastases and 2 were Grade 2, and 1 Grade 3. They died at eight months, eighteen months, and forty-five months, respectively. Their lives were perhaps prolonged to some extent.

There were no appareat metastases in 10 patients, 7 of whom are living: 1 at three and one-half, 4 at five and one-half, and 2 at six years. Five were Grade 1 and 2 Grade 2. The other 3 died as follows: 1 at one and one-half years from a metastasis in the brain, 1 at two years with a mediastinal metastasis, and 1 at six years with a lung metastasis, all Grade 1.

Six patients had no evident metastases but the tumor was ruptured during removal. Four of them are well at four, four, five, and five years, respectively, all Grade 1. Another patient with Grade 1 is alive with disease at four years and a patient with a Grade 2 died in nine months.

Sixteen (55 per cent) are apparently well, 1 is alive with disease, and 12 are dead. The series is too small and the time too short to draw accurate conclusions. Fifty per cent were Grade 1 as against 32 per cent for the whole series of 149 cases, so the survivors had a low grade of malignancy. It is sensible to continue the method when of 6 patients with evident metastases in the pelvis 2 have lived five years and are apparently well. We think that where there are general metastases the disease recedes to some extent for a few months.

It is also possible to make apparently inoperable tumors operable by giving x-ray treatment first, as shown by Baer and others.

We believe that the peritoneoscope may be of value in the diagnosis of early cases, but we find it difficult to obtain a view of the bottom of the pelvis. The most important factor in getting better results in this disease is earlier diagnosis, for we all know that most of the cases become incurable before definite symptoms arise. Preventive examinations may reveal the presence of small tumors and treatment may be instituted early, but there are evidently cases with an everting type of papillary cancer which spread across the pelvic peritoneum without forming a palpable tumor. There is a sense of thickening to the trained examiner, and the patient sometimes complains of a vague discomfort or feeling of pressure in the pelvis. The peritoneoscope should reveal such growths, and treatment by operation and x-ray should be started early enough for some cures. The peritoneoscope is useful in discovering the extent of the disease. We have the feeling that because such a large percentage (47 per cent) die within the first two years after operation it might save a patient a useless operation and convalescence if she were not operated upon if the peritoneoscope showed generalized metastases

throughout the abdomen. Twenty-seven of our patients had general abdominal metastases and only 4 survived for more than two years. They died at three and three-fourths, four, four and one-half, and eight and one-half years, respectively. Most of the rest died within a few months, only 3 living more than a year. One cannot advocate no treatment, however, because such patients have nothing to lose and operation may prolong life in a few.

SUMMARY

Cancer of the ovary should be treated by as radical an operation as circumstances permit and that should be followed by x-ray treatment.

Preoperative x-ray treatment may make some apparently inoperable cases operable.

The omentum should be removed as a routine.

The solid and semisolid tumors are much more malignant than the mostly cystic ones.

The gross extent of the disease determines the prognosis but, other factors being equal, those of low malignancy survive longer.

The results of treatment are poor because the tumor grows silently until it is incurable in from 36 to 50 per cent of the cases.

Earlier diagnosis is essential and can be made only by preventive examinations.

REFERENCES

Lynch: Am. J. Obst. & Gynec. **32:** 753, 1936. *Halban and Seitz:* Biology and Pathology of the Female **5:** 675, 1926. *Meigs:* South. M. J. **30:** 133, 1937. *Baer:* Arch. Path. **26:** 240, 1938. *Sampson:* Am. J. Path. **14:** 385, 1938. *Boyd:* General Pathology, 1938.

DISCUSSION

DR. JOSEPH L. BAER, Chicago, Ill.—There are two points in Dr. Pemberton's paper, which I should like to emphasize. First, I find grading largely futile. For example, there was a type of carcinoma of the ovary which formerly was known as the small cell carcinoma of the ovary and which, under the microscope, has the appearance of utmost malignancy. Nevertheless, it is a relatively benign growth in the ovary which, in today's nomenclature, is known as a disgerminoma. On the other hand, I reported in the anniversary number of the *Archives of Pathology,* dedicated to Dr. Ludwig Hectoen, an instance of a patient who had upon operation a literally inoperable abdominal condition, with bilateral solid ovarian tumors, with metastatic nodules all over the peritoneum and viscera, and extensive omental involvement. The condition was quite inoperable, but biopsy revealed a completely benign picture. This patient was subjected to vigorous roentgen treatment and after a number of months was operated upon again. It was found that there had been a complete disappearance of all the metastatic nodules, including nodules in the liver. The genital field was entirely operable. After operation the patient was subjected to further irradiation and is now entirely well. Experience with such cases makes me feel that microscopic grading has very little value so far as the prognosis or type of treatment is concerned.

Dr. Pemberton spoke of the routine resection of the omentum, which he considers to be useful for the prolongation of life and possibly to produce a cure. The omentum physiologically serves to cover the abdominal viscera but is not a shelter for the pelvic peritoneum, consequently metastases from the ovaries can readily reach the pelvic peritoneum. In the absence of the sheltering omentum overlying the abdominal contents, these metastases will be prone to invade the viscera directly. That may be of little consequence except for the fact that in our experience, which

has been largely with autopsy material most of the deaths have been due to intestinal obstruction. Consequently, my own feeling at the moment is that unless the omentum is involved at the time of operation it is better left in situ.

As to treatment, obviously surgery, immediate and as completely radical as is feasible, in every instance in which carcinoma of the ovary is diagnosed or suspected, is the primary indication. Thereafter the patient should receive the maximum of irradiation, which is even more important than the surgery.

Our technique with the radium bomb consists in the administration of 40,000 mg. hours to each of four pelvic fields, for a total of 160,000 mg. hours with 1 mm. of platinum filtration at 10 cm. distance. X-ray therapy is carried out on the 200 kv constant potential machine with Thoraeus filtration (equivalent to 2 mm. copper), 2,000 r. units being administered to four pelvic fields for a total of 8,000 r. units, measured on the skin.

In conclusion, I regret to announce that in the last five-year group we have only one authentic survival, both in our tumor clinic and in the private practices of the sixteen men in our department.

DR. EMIL NOVAK, Baltimore, Md.—The particular value of Dr. Pemberton's study lies in the fact that he has eliminated from his group certain types which are of relatively low malignancy. These include particularly the rather frequent granulosa cell carcinoma, the less frequent disgerminoma and the rare arrhenoblastoma. Any series which includes any considerable number of this group should show much better results than pertain to ovarian cancer in general. Dr. Pemberton has avoided this error.

I was rather surprised that he classed only six of his 140 cases as solid carcinoma, and I presume that this must be due to the fact that his rather large group of "semisolid" tumors must include any solid neoplasms which have undergone cystic degeneration, and become in that sense semisolid. Strictly speaking, however, they should be grouped as solid carcinomas, which in the figures of most laboratories would be about two-thirds as common as the cystic variety of ovarian cancer. The whole question of ovarian tumor classification is still very confused, and it might be a fine thing for this Society to devote one of its sessions some time to a discussion of this subject, in an effort to arrive at some sort of satisfactory working classification.

I was particularly interested in one of Dr. Pemberton's slides because it illustrates what I believe to be the usual channel of spread of ovarian cancer to the endometrium. This slide showed an intact endometrium, and immediately beneath it a carcinoma nest in a lymphatic. Such a small carcinoma area is likely to destroy and replace the overlying endometrium, so that it might give the impression that carcinoma particles have implanted themselves on the uterine mucosa. While this is a theoretical possibility, I believe that it is far less common than the lymphatic route of dissemination.

With reference to the matter of histologic grading, it would seem to me to be expected that this would be less valuable with the varied group of ovarian cancers than in the evaluation of tumors of one histogenic type. Ovarian cancer is of multiple and in most cases unknown histogenesis, so that systems of grading might be expected to be of comparatively little value in the present state of our knowledge.

Dr. Pemberton's suggestion concerning removal of the omentum would seem a wise one when the omentum extends into the pelvis, or when it is adherent to the ovarian tumor. On the other hand, where the omentum is very short and in the upper abdomen, this procedure would not seem essential.

DR. RICHARD W. TE LINDE, Baltimore, Md.—There is no field in gynecology in which the prognosis is more uncertain than in ovarian tumors. This is true both from the clinical standpoint and from the standpoint of microscopic pathology. Ten years ago I saw a woman with a massive recurrence of an ovarian neoplasm, and it seemed that it would be but a short time before she died. She was given deep x-ray therapy, and I saw her a month ago clinically well with complete absence of the pelvic mass. The tumor corresponded microscopically to Schiller's so-called mesonephroma. I wonder whether all of this special group of tumors which we now recognize as an entity will prove to be so radiosensitive.

Apropos of the question of the omentum, two years ago I operated upon a woman with a pseudomucinous cyst with gross malignant change in many places. The omentum was carcinomatous and three or four inches thick. I removed the tumor together with other pelvic organs but left the omentum in situ. I saw the woman again last week and she was clinically well. The omental mass had shrunken so that it could not be palpated abdominally. One wonders if her omentum had not been there whether the intestines would have been involved as the omentum was, in which case she would have had a chance of an obstruction. The disappearance of this omental mass after removal of the parent tumor emphasizes the point made by Dr. Pemberton of the advisibility of removing the tumor grossly even when one obviously cannot remove every bit of the neoplasm.

I should like to mention finally three very illuminating cases of granulosa cell tumor which recurred thirteen, sixteen, and twenty years after the original operation. In all three cases we have biopsies of the recurrent tumors, and in each instance, the microscopic picture of the recurrent tumor is identical with that of the original growth. Five-year "cures" of granulosa cell tumors do not by any means indicate a permanent cure.

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—Dr. Pemberton's figure of 32 per cent cure is not only very encouraging, but is actually one of the best ever reported on any considerable number of cases of ovarian cancer. On the other hand, I am more or less convinced that any such figure requires careful scrutiny.

Ovarian carcinoma is such a miscellaneous group that it is probably incorrect to report on it as a whole. In this respect Dr. Pemberton has made a real contribution in separating the granulosa cell tumors from his series. There is, however, another group of tumors where inclusion or exclusion will largely affect the end result figures. There are a large number of tumors on the histologic borderline between the benign papillary cystadenomas and the malignant cystadenocarcinomas, and in our experience it is in this group that most cures of so-called cancer of the ovary are found.

In spite of several opinions expressed today to the contrary, grading to the extent of recognizing this type of questionable malignancy is of vital importance in prognosis and statistics. You are familiar with the cystadenoma which produces implants that eventually disappear. This type is morphologically quite similar to the adenoma malignum of the endometrium which experience shows should be classed as cancer. A similar tumor in the ovary has, however, almost always a benign course.

It is of vital importance then in interpreting statistics on carcinoma of the ovary to know what histologic standards have been set by the writer.

Our own experience at the Roosevelt Hospital in New York illustrates this point. In 1929 we reported about 8 per cent of five-year cures. We went over the new material a year ago, accepting at first the pathologist's routine diagnosis for classification, and found that with the recent cases the five-year cure rate had risen to about 25 per cent. When we reviewed the slides, however, we discovered that about 7 out of 10 new five-year cures were tumors of a high degree of differentiation and of doubtful malignancy. With these subtracted we were back to the old figure.

Until there can be some standardization of the histologic criteria of malignancy in the ovary, results obtained by different clinics or by rival methods of therapy cannot be satisfactorily compared.

DR. WILLIAM P. HEALY, New York, N. Y.—Until comparatively recently the operator has seldom waited for the opinion of a pathologist on the gross specimen before deciding to limit the removal to the adnexa of one side. If the adnexa are involved on both sides, of course, we do not need to wait for that opinion but with one side apparently normal it is our custom to send the total specimen to the pathologist or have him present as consultant, so that we will know immediately what operative procedure is indicated. Often we have patients sent to us after a previous operation in which only one side has been removed, but within another year or so the other side has become involved.

Roentgen ray is the only form of therapy we can use, aside from surgery. Radium is of little value unless used in a pack and that is not a very facile form of

application. We feel that high voltage roentgen ray is better because it can be spread over a larger area and more tissues can be included. X-ray therapy is usually a palliative rather than a curative measure. Yet if we believe from the physical examination of the patient that the lesion is carcinoma of the ovary, the patient is subjected first to preoperative roentgen irradiation rather than to operation first followed by postoperative irradiation. The results are much better if the irradiation is used first in the majority of instances.

DR. FRED L. ADAIR, Chicago, Ill.—Dr. Taylor has emphasized that we must be extremely careful in evaluating statistics on curability. There is great difficulty first in interpreting the histologic picture and deciding whether it is or is not malignant in certain of these cases. Second, because we are frequently dealing with a very large tumor from which a small area is selected for microscopic examination, we may miss an area which is malignant.

DR. PEMBERTON (closing).—Since the publication of the program, I have done much more work on the paper. There are 149 instead of 122 cases and the five-year salvage is 32 per cent instead of 22 per cent.

Grading depends largely on a personal equation. There is such a multiplicity of etiology in these tumors, as Dr. Novak says, and they vary so much in their histology that I do not believe you could have a real standard that would work in several different clinics.

It is also true that 69, or 47 per cent, of these patients died within two years after the original operation. Hence I wonder whether it is worth while to operate on patients who have general abdominal metastases? We have not tried preoperative x-ray treatment.

As to the omentum, my idea was that it might have microscopic metastases in it. I agree also that most of these patients die of intestinal obstruction, and it is not so important whether you leave it in or remove it. It might be better to leave it in if it appears normal, but certainly if there is any suggestion of metastasis it would be better to remove it.

As to irradiation, we start three weeks after the operation and do not irradiate patients in poor condition because the toxemia they get from it may tip the scales.

As to the semisolid tumors, I call the adenomatous ones with solid masses in them semisolid, and the medullary ones are solid. Here again is a personal classification which is difficult to define.

These tumors are silent and sometimes do not cause symptoms until they are quite far developed. In our series 36 per cent were incurable when first seen. Preventive examinations are necessary in order to make early diagnoses, but in all of the preventive examinations I have done, I have found only one ovarian tumor and that was in a woman who came in a year after a negative examination, and who had at that time a benign serous cystadenoma.

As regards grading, Dr. Taylor suggested that most of the survivors were probably in Grade I. This proves to be true, for 26 (70 per cent) were graded at I, 10 (27 per cent) at II, and only one (3 per cent) at III. This last patient died in the sixth year after operation for cancer. Therefore the degree of malignancy plays a part in the prognosis; but here, as in cancer of the cervix, the gross extent of the disease is the usual determining factor.

CANCER OF THE VULVA*

An Analysis of 155 Cases (1911-1940)

Fred J. Taussig, M.D., St. Louis, Mo.

IN STUDYING the clinical aspects and methods of treatment of a disease that is as relatively infrequent as cancer of the vulva, the observer whose experience is limited to less than twenty cases can hardly venture on an opinion. My first paper written in 1917 was based on only 15 cases. In the course of the succeeding years from my service at the Barnard Free Skin and Cancer Hospital and in private practice that number has now increased to 155, a total which compares favorably with the reports from larger clinics in this country and abroad and justifies, I believe, some rather definite conclusions as to etiology, incidence of gland metastasis, and the relative value of radiologic and surgical methods of treatment.

These cases may be divided into five-year periods as shown in Table I.

Table I

1911-1915	8 cases
1916-1920	19 cases
1921-1925	26 cases
1926-1930	31 cases
1931-1935	27 cases
1936-1940	44 cases

I have not included in this series of 155 cases, 3 cases of sarcoma of the vulva and one early case of melanoma situated in the pubic region. Three other cases of melanoma originating about the labia and urethral meatus have been included. Twelve cases of periurethral cancer were also classified as vulvar lesions since the exact point of origin of the neoplasm could not always be determined, especially in the more advanced cases. In one patient the small labial tumor proved to be an adenocarcinoma, probably of sweat gland origin. With the exception of three adenocarcinomas springing from Bartholin's gland, the remaining tumors were carcinomas of squamous cell type. The histologic picture varied greatly. Elsewhere the histopathologic changes in these cases will be more fully discussed. Suffice it to say that the lesions varied in malignancy from small well-differentiated papillary nodules in which a positive diagnosis could only be established after careful study, to tumors in which the loose-structured undifferentiated appearance of the tumor cells resembled the picture of a sarcoma. The former relatively benign lesions usually originated from the skin of the labia or prepuce; whereas the more malignant lesions usually arose from old syphilitic vestibular ulcers or from the glans of the clitoris. Cancer of Bartholin's gland occupied a more intermediate position.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

From an anatomic viewpoint I have tried to separate the 155 cases according to site. Some writers had differentiated between labia minora and majora, perineum, and clitoris. In Table II, I have preferred to include under one head as epidermal, the entire vulvar skin including the prepuce. As stated in previous papers, many cases of typical preputial cancers are called clitoris cancer. Almost always such tumors start from an area of preputial leucoplakia and not from the clitoris itself although the latter may be secondarily involved. True clitoris cancer is very rare. Besides the group of periurethral and Bartholin gland cancers, we have cases springing from the more delicate epithelium of the vestibule of the vagina. Table II shows this anatomic subdivision of cases:

TABLE II

Epidermal	104 cases
Vestibular	11 cases
Periurethral	12 cases
Bartholin gland	9 cases
Glans clitoris	2 cases
Unclassified (advanced cases)	17 cases

Coming now to the important question of lymph gland metastasis in carcinoma of the vulva, we find that in 88 out of the 155 cases observed there was evidence of carcinoma either in the form of large hard fixed glands in the advanced inoperable cases or in microscopic evidence of such metastasis in those patients subjected to a partial or complete excision of the lymphatic chain. This would make 57 per cent of the total cases. With the certainty that a certain number of smaller metastases are doubtless overlooked when serial sections of all glands are not made, it seems fair to reiterate a statement previously made that approximately two-thirds of vulvar cancers are complicated by lymph gland metastasis.

When we list only the cases subjected to lymph gland removal, we find the incidence of metastasis somewhat lower. In the group of one-sided incomplete or superficial gland operations, we note that in 18 out of 27 such instances (66.6 per cent), cancer was present microscopically. In the less advanced cases subjected to a complete Basset operation, cancer was found present in only 28 out of 68 cases, an incidence of 41 per cent. Adding these two groups of operative cases together we find:

Carcinoma present in glands	46 times
Carcinoma absent in glands	49 times
Percentage of cancer metastasis	48.4

Extension of the disease to more distant lymphatics was relatively infrequent. However a considerable number of the terminal cases showed involvement of the lungs, the abdominal organs and even in one case the brain. Unfortunately relatively few of the terminal cases died in hospitals where an autopsy could be secured. Hence, the information on this point has but little value.

MULTIPLE CANCERS

Of special interest in the analysis of this group of cases is the relatively high incidence of double cancers. I have not included under

Fig. 1.—*A* and *B* show epidermal carcinoma of the vulva on a basis of leucoplakic vulvitis; *C*, case of periurethral carcinoma; *D*, vestibular carcinoma on a syphilitic basis.

this head four cases in which a new cancer appeared many years after excision of the primary tumor upon a remaining island of leucoplakic skin. These were all patients in whom a cancer had developed on the basis of a leucoplakic vulvitis with kraurosis. The primary tumor was

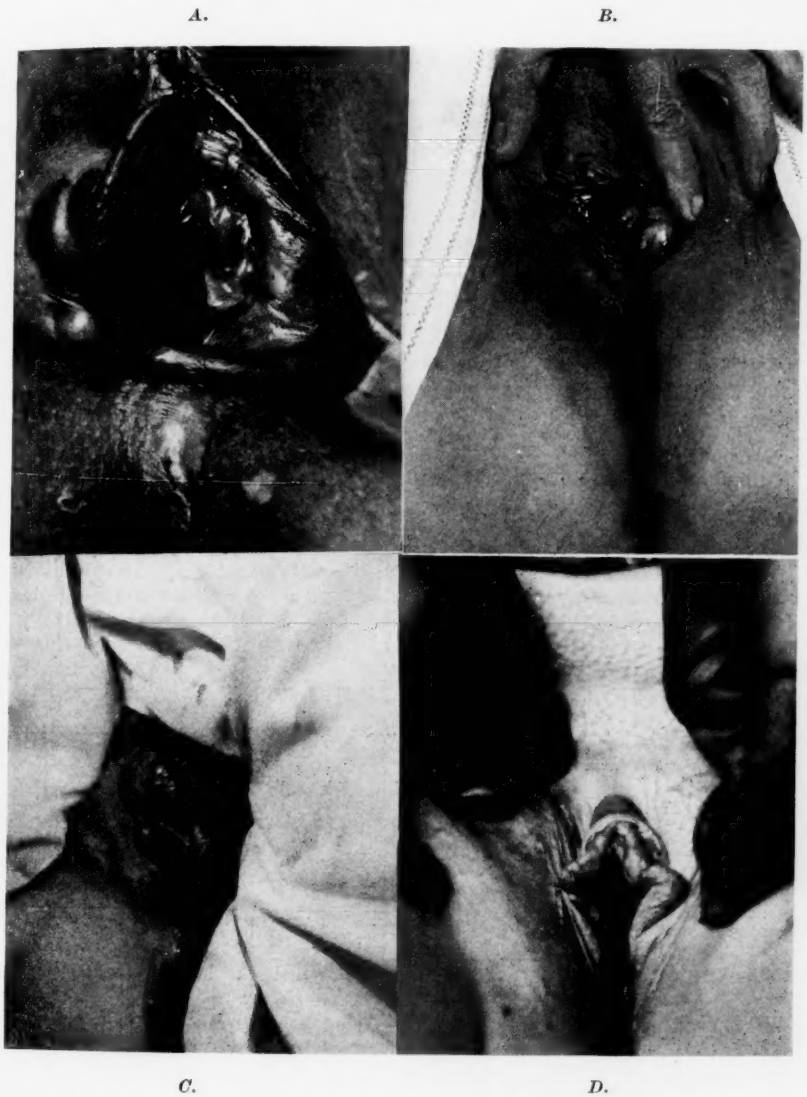

Fig. 2.—*A* and *B* are examples of carcinoma of Bartholin's gland; *C* and *D* are cases of primary carcinoma of the glans clitoris.

either on the prepuce or the upper labial region. The vulvectomy did not include the perineoanal region, and the new cancer usually developed in this area on a leucoplakic area as a superficial lesion and not in the vulvar scar. In addition to such local new cancers, we find the following incidence of cancer in other organs, either before or after

the appearance of the vulvar carcinoma. In each instance the possibility of interpreting these cancers as metastasis was carefully eliminated.

Cancer of the cervix, 3 cases (2 before, 1 after vulvar carcinoma)
Cancer of the breast, 2 cases (1 before, 1 after vulvar carcinoma)
Cancer of the head and neck, 5 cases (3 before, 2 after vulvar carcinoma)

In a recent communication read at the meeting of the American Society for Cancer Research, Shields Warren analyzed the cases of multiple malignancies from several Massachusetts institutions and found that in a series of 1,149 cases of cancer of the skin, there were 77 patients, who at some time showed evidence of cancer in other organs of the body. This incidence of 6.7 per cent was over twice as high as the normal expectancy, 3.1 per cent, of such a combination of the two cancers. The occurrence of 10 such double cancers in 155 vulvar malignancies, or 6.4 per cent, in my series corresponds rather closely to Dr. Warren's figures. The development of a satisfactory statistical formula to express accurately the difference between the expected and actual incidence of multiple cancers in this vulvar group is difficult because of the small total number of cases involved. Clinical observations such as these, however, point to an important somatic factor in the causation of cancer.

GENERAL STATISTICS

Age.—The average age of the 155 women in this group was 58 years. This is slightly less than the 60.9 years recorded by Folsome in his recent report of 126 cases from the University of Michigan clinic. When we analyze this age incidence more closely, however, we find in our series that 88 patients were over 60 years of age and only 67 were under 60. Table III shows patients grouped by decades.

TABLE III

24-29 years	4
30-39 years	17
40-49 years	23
50-59 years	23
60-69 years	54
70-79 years	31
80-87 years	3

The oldest patient was 87 years, the youngest 24 years. A highly malignant sarcoma of the vulva not included in this series was found in an infant five months old.

The age incidence of the five-year survival cases was 55 years, indicating that the malignancy of the disease does not decrease with the age of the patient. All 12 operative deaths in this series of 155 patients occurred in women over 60 years, with an average age of 68 years.

Symptoms.—Pruritus was noted as the outstanding symptom which caused the patient to come for examination in 42 cases. In many other instances, it was also noted but in addition to this the occurrence of a lump or an ulcer or sore was the primary reason for the patient's consultation. A bloody discharge or burning on urination was occasionally stated as the outstanding symptom. Table IV shows the frequency of these symptoms.

Duration of Disease.—In no form of genital cancer do we find more evidence of inexcusable delay in seeking medical advice than in cancer of the vulva. This delay is only too often increased by failure in diagnosis or improper advice on the part of

TABLE IV

Lump in vulva	46
Pruritus	42
Sore on vulva	26
Burning on urination	24
Blood-tinged discharge	22
Insufficient data	4
Counted twice	9

the family doctor. It is to be hoped that cancer educational work may in the future be extended to include this form of malignant tumor. Here are the figures of the interval between onset of symptoms and competent medical advice. I have not included, as a part of this elapsed time, cases in which a leucoplakic vulvitis had existed for many years previous to the development of the cancer.

TABLE V

Less than three months	7 cases
3-6 months	48 cases
7-12 months	24 cases
13-24 months	34 cases
Over 2 years	24 cases
Insufficient data	18 cases

Were it not for the fact that cancer of the vulva is of relatively slow growth as compared with cervix or vaginal cancers, few cases would be curable.

I was amazed to find on analysis of these 155 cases how many patients had tried pastes or salves or had been given inadequate surgical or radiologic treatment before coming to us for advice. Thirty-one such instances were noted (20 per cent of the total). In 22 patients a local excision of the nodule had been made, three times in combination with an inadequate radium or x-ray treatment. In 4 cases radium or x-ray was alone applied. Twice the nodule was cauterized. In two other cases caustic pastes or salves were applied and one patient tied a string around the pedicled tumor. In spite of all this preliminary malpractice, it was surprising that we succeeded in obtaining 7 five-year survivals in this group.

Etiologic Factors.—In previous reports I have discussed more fully the etiologic factors that may possibly predispose to the development of cancer of the vulva. In many instances the extent of the disease makes it impossible to put our finger on the underlying factors of local irritation, but, all in all, the presence of a preceding pathologic condition is very common as shown in Table VI.

TABLE VI

Leucoplakic vulvitis	72
Syphilitic or postsyphilitic ulcer	9
Senile warts	6
Bartholin abscess	4
Urethral caruncle	3
Trauma	3
No definite pathology	58

Of undeniable importance is the occurrence of a leucoplakic vulvitis in almost one-half of the cases. It was an underlying factor in 72 out of 104 cases of epidermal cancer. A pre-existing syphilis was noted in 9 out of 11 vestibular cancers. Bartholin infection was definitely noted in 4 out of 9 Bartholin gland tumors.

PREVENTION

What has been stated regarding etiologic factors raises the issue: How often can we prevent the development of a cancer of the vulva?

I am convinced that we have been very remiss in our preventive measures in the past. The incidence of vulvar carcinoma might very possibly be cut in half, if we would adopt the following measures:

1. A complete vulvectomy in cases of well-developed leucoplakic vulvitis, and rigid supervision, at least twice a year, in milder cases where the patient refuses operative treatment.

2. Intensive antisyphilitic treatment in tertiary lesions of the vulva, especially in negroes.

3. Removal of vulvar warts in women past the menopause.

4. Close observation or excision of enlarged Bartholin glands in women over 40 years of age.

5. Cautery excision or radiant treatment of urethral caruncles.

Particularly in leucoplakic vulvitis would I stress the advantages of surgery over nerve resection or treatment with ovarian hormones. The latter undeniably often decreases the pruritus, but the question whether the use of such carcinogenic substances may not at times predispose to the development of a cancer might very well be raised.

In connection with the relationship of leucoplakic vulvitis and cancer, I would cite three interesting observations, one of which comes from the practice of Dr. W. P. McNalley, to whom I am indebted for the privilege of using it.

CASE REPORTS

CASE 1.—Mrs. Y. G. had had symptoms of vulvar itching with skin changes that had been treated by a dermatologist twelve years ago when she was 67 years old. Ten years later she was seen by a gynecologist, the condition was diagnosed as leucoplakic vulvitis, but because of her age and a cardiorenal condition, anesthetic salves alone were prescribed for the relief of her pruritus. At this time the vulva showed the typical picture of a leucokraurosis without any ulcers or suspicious thickening anywhere. Fifteen months later, she noticed a small lump which slowly increased in size in the following nine months. When I was called in consultation by her physician, Dr. Leon Foster, she had an elevated plaquelike cancer 4 cm. in diameter in the right labial region with a parchmentlike leucoplakia of the entire vulva. Since she was then 79 years old and had a bad heart, a simple vulvectomy was done. Her immediate condition was good, but she suddenly died on the fourteenth postoperative day of coronary embolism.

CASE 2.—Mrs. M. S. was operated upon by me at the age of 60 years for a leucoplakic vulvitis of long standing. A vulvectomy was done, but the pruritus returned one year later at a point just beyond the area of skin removed. Unfortunately the patient did not return for re-examination as she had been instructed. She was not seen from Sept. 30, 1930 until Nov. 25, 1936. By this time she had developed an epithelioma 4 cm. in diameter in the right labial region with evidence of leucoplakic change about it and the perineal region. The radical vulvectomy and double-sided Basset lymph gland removal was followed by a severe local infection, aggravated by an acute cholecystitis, and death occurred fourteen days after operation.

CASE 3.—Mrs. K. M. (private patient of Dr. McNalley) consulted him in June, 1935, for pruritus vulvae. On Oct. 29, 1935, a vulvectomy was done for a typical leucoplakic vulvitis. Microscopic examination at this time showed no evidence of cancer. In March, 1936, she was entirely well. She did not return for further observation until July 25, 1938, when examination showed a tumor 6 cm. in diameter in the right labial region rising from a remaining island of leucoplakia. The inguinal glands on the right side were enlarged and hard. A right-sided Basset

operation was done and radium applied locally. The inguinal glands showed cancer. There was rapid extension of the disease and the patient died three months later.

Cases such as these teach the lesson, I think, that patients with leucoplakic vulvitis, even if operated upon radically, should be kept under close observation throughout their life and warned to return on the slightest appearance of an ulcer or lump. The close etiologic relationship between this condition and cancer is certainly emphasized by such reports as these.

Stage of the Disease.—The classification of cases according to the stage to which the cancer has progressed is of value in determining the indication for, and the results of, treatment. D. den Hoed puts cases that are recurrent after previous treatment in a special class, but in view of the reasonably favorable results obtained by him and by myself in this group, I cannot see that it has any special value. The following classification seems practical:

Group I: Patients without palpable metastasis, tumor 1 to 3 cm. in diameter.
Group II: Patients without palpable metastasis, tumor 4 to 7 cm. in diameter.
Group III: Patients with tumor over 7 cm. in diameter, or smaller tumors with evident but still movable metastasis.
Group IV: Patients with extension to the vagina or subpubic space or with large fixed lymph glands.
Group V: Far-advanced cases with broken down lymph glands and cachexia.

The determination of lymph gland metastasis is not easy of diagnosis before operation. In practically every case, a few enlarged lymph glands can be felt in the groin. Only when they are over 3 cm. in diameter and hard can we say with reasonable certainty that a metastasis is present.

Analysis of the 155 cases in my series according to clinical groups is given in Table VII, together with a similar analysis made of the 128 cases reported by Folsome from the University of Michigan clinic.

TABLE VII

TAUSSIG			FOLSOME		
GROUP	NUMBER	PER CENT OF TOTAL	GROUP	NUMBER	PER CENT OF TOTAL
I	28	18	I	10	8
II	48	31	II	22	17
III	43	28	III	40	31
IV	29	18	IV	43	34
V	7	5	V	13	10
Total	155			128	

From these figures it would seem that Folsome's cases were somewhat more advanced than mine, which may in part account for the lower survival rate in his series.

TREATMENT

In the course of the years from 1911 to 1940 certain changes have occurred in the method of treatment, but on the whole a fairly consistent plan has been observed in the past two decades varied only by

the extent of the disease in the particular case. Surgical measures were employed in all but 38 of the 155 cases. Radium and x-ray were early employed in some cases but in recent years have been almost wholly abandoned, owing to unsatisfactory results and painful sequelae. Table VIII shows the division of cases according to the therapeutic measures employed.

Fig. 3.—*A*, Group I carcinoma of the vulva; *B*, Group II infiltrating carcinoma of the vulva; *C*, Group II epidermoid cancer of the prepuce; *D*, Group III cancer of the left labia.

Although 117 of the 155, or 75.5 per cent, were subjected to surgical excision of the tumor with or without the tributary lymph gland chain, this hardly represents a true picture of the operability, since, in a certain number of the vulvectomies, the procedure was definitely merely

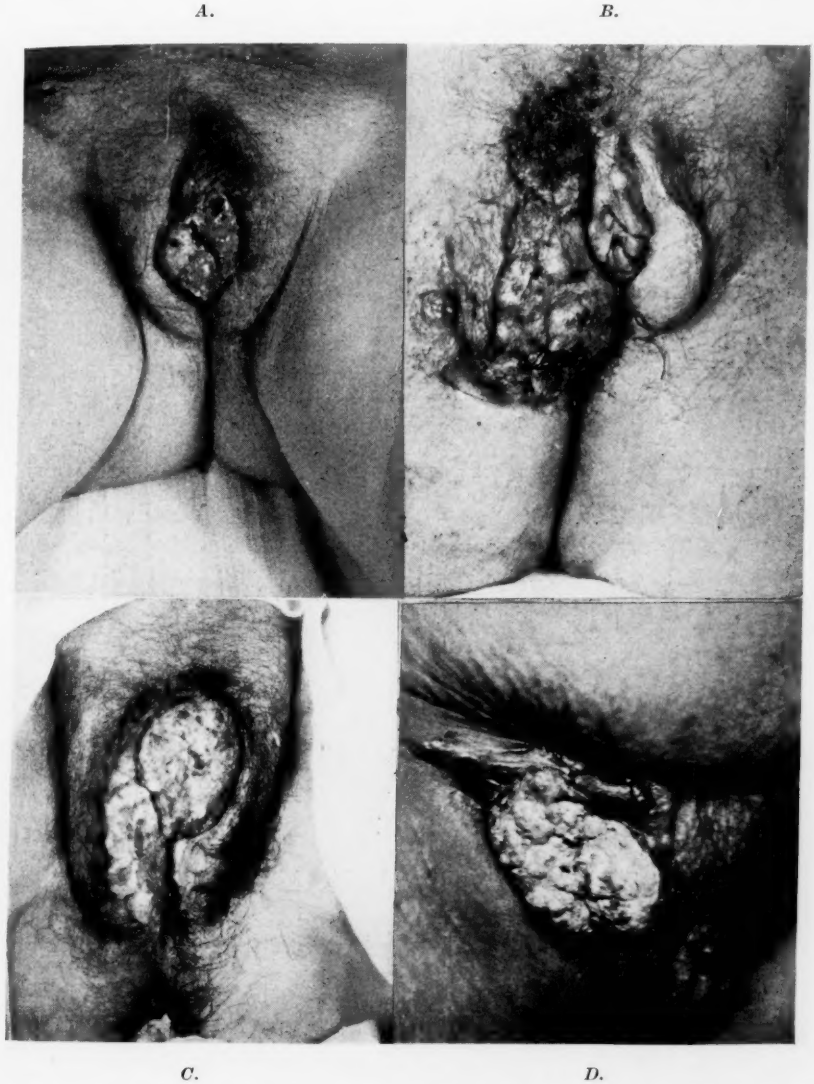

Fig. 4.—*A*, Group IV vulvar carcinoma with indurated adherent gland in right inguinal region; *B*, Group IV labial cancer with extension to the perirectal and subpubic space; *C*, Group IV cancer of the vulva with extension up the vaginal canal; *D*, Group V cancer of the vulva with large necrotic adherent lymph gland metastasis.

a palliative procedure. I am convinced, however, that many surgeons have in the past considered cases inoperable that in our experience are not only technically removable but even give a fair chance for a five-year survival. I think it therefore no exaggeration to say that as a

TABLE VIII

Complete Basset operation with vulvectomy	68
Incomplete or superficial gland removal with vulvectomy	27
Vulvectomy	22
Radium or deep x-ray therapy	22
Palliative measures	7
Refused treatment	9
	155

rule 70 per cent of cancers of the vulva are surgically operable. If we consider only the epidermal cases this percentage would be considerably higher.

OPERATIVE MORTALITY

The mortality varies primarily with the age and physical condition of the patient rather than with the extent of the operation as seen in Table IX.

TABLE IX

	CASES	DEATHS	PER CENT
Complete Basset with vulvectomy	68	5	7.35
Incomplete gland removal with vulvectomy	27	3	11.1
Vulvectomy only	22	4	18.2

The higher mortality in vulvectomies was due primarily to the age incidence. The average age of the four women who died after vulvectomy was 72 years. Even more striking are the figures in the cases where a complete Basset operation was done. Out of 45 Basset operations in which the patient was under 65 years, there was only one death (2 per cent); whereas in the 23 Basset operations done on women over 65 years, there were four deaths (18 per cent). This clearly shows that any surgical procedure, and especially the extensive Basset operation if done in such extremely old women, is bound to be attended by a high mortality. In the 5 operative deaths following the Basset operation, the cause was: pneumonia, 3 cases; pulmonary embolus, 1 case; septic infection with cholecystitis, 1 case.

Basset Operations.—This radical, double-sided, lymph gland removal with vulvectomy was done in 19 out of the 28 Group I cases, in 31 of the 48 Group II cases, in 17 out of the 43 Group III cases, and in one Group IV case. The reason for not doing more Basset operations in the Group I and II cases was partly because of the physical condition of the patients, and partly because for many years my service at the Barnard Free Skin and Cancer Hospital was shared by Dr. Gellhorn, who pre-

TABLE X

	CASES	CANCER IN GLANDS	PERCENTAGE INVOLVEMENT
Group I	19	4	0.21
Group II	31	13	0.42
Group III	17	10	0.59
Group IV	1	1	
Total	68	28	0.41

ferred to do a superficial or one-sided gland removal in cases of vulvar carcinoma. Lymph gland metastasis in relation to the various groups in Basset operations was as shown in Table X.

Points in Technique.—Originally I followed closely the method described by Basset including a single incision from one iliac spine to the other and including the entire vulval mass. Also I routinely cut both Poupart's ligaments to gain access to the area in the femoral ring. In the course of the past twenty years, I found that the complications of wound healing with wide separation of the wound edges made it desirable to make three incisions, one over each groin and one over the vulva, retaining a bridge of normal skin between them to prevent too wide a gaping of the postoperative wound. Retention of this bridge of skin did not lead to recurrence at this point. I also found that in all but a very few cases all lymphatic glands could be cleanly excised without actually cutting Poupart's ligament, hence this was omitted, as adding to the risk of hernia. Another important change was the angle

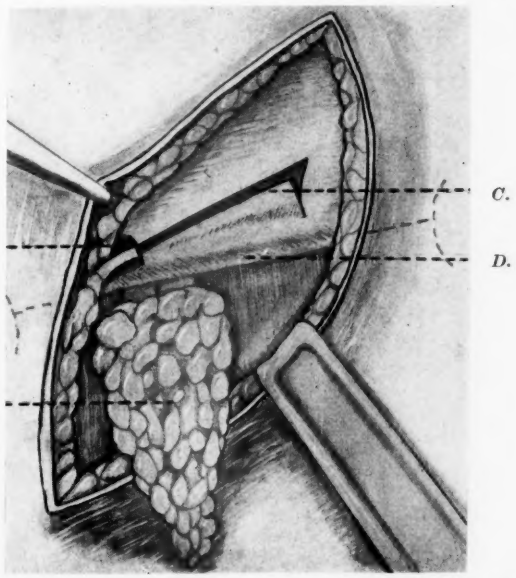

Fig. 5.—Right-angled fascial incision over the inguinal canal in Basset operation. *A*, External inguinal ring; *B*, superficial inguinal lymph gland mass dissected free; *C*, obturator internus muscle; *D*, Poupart's ligament.

of the inguinal incision. Instead of having it run almost parallel to Poupart's ligament, it is now being made at an angle of 60 degrees to this ligament, thereby aiding to preserve the nutrition of the edges of the inguinal wound. The incision goes as far as the lowest point of Scarpa's triangle, permitting the more complete removal of fat and lymph glands surrounding the deep saphenous vein. I have also extended the deep exploration of the obturator region, from which one or two good-sized glands are invariably excised. The additional removal of the hypogastric gland, as suggested by E. Kehrer, requires a far more extensive primary incision, and, considering the resulting higher postoperative mortality and the very rare involvement of this gland, does not seem justified.

Another change in technique which I have adopted is the right-angled cut through the transversalis fascia. This cut follows the course of the inguinal canal from the external inguinal ring to a point over the internal ring and then proceeds from there at right angles to Poupart's ligament. By turning down this fascial flap, access to the external iliac glands is more readily obtained.

The inguinal wounds are always drained, usually through a separate slab incision at the lowest point of drainage in Scarpa's triangle. Of importance is the applica-

tion of a firm compression bandage over the inguinal wound so as to eliminate as far as possible dead spaces with the tendency to retained secretions. Only in rare instances have I been able to secure primary wound healing. Varying changes of technique have failed to prevent the frequent occurrence of necrosis in the wound edges associated with a moderate wound infection. This has, I find, been the general experience of other operators and is doubtless due largely to the poor vitality of tissues in this region in older individuals.

In the technique of vulvectomy, I have stressed a wide excision of the vulva, including all the perineal skin in cases associated with leucoplakic vulvitis. Attempting to close this large defect by skin flaps from the thighs has proved impractical, owing to poor wound healing. Hence, I have usually left a considerable defect in the vulvar wound to be closed by granulation. The perineal defect can, however, be readily covered with a posterior vaginal flap. The vulvectomy is best done with the diathermy knife and the wound edges subsequently trimmed off with the scalpel. In a few cases of urethral or subpubic involvement, radium has been placed in the open wound or urethra for a suitable dosage. The postoperative wound is exposed to light and kept as dry as possible to prevent maceration.

One of the complications of this extensive procedure has been the length of time required for the operation. Local anesthesia, occasionally supplemented by small amounts of ether narcosis, has usually been employed to diminish operative shock. Some time has been saved in the inguinal dissections by dividing my assistants into two teams, one working on each side. In 37 instances the operations were done in one stage (usually early cases), and in 31 patients a two-stage operation was done. In not a single case did the operative death occur earlier than the sixth day after operation.

In the after-care we would stress measures to secure proper drainage of the inguinal wounds, and the early establishment of a semi-Fowler position of the body to diminish the chances for pneumonia. When sloughing has occurred, the wound edges should be trimmed; and after clean granulations have been formed, pinch grafts should be taken from the thighs to produce epithelialization of the wound defect.

Five-Year Results.—To obtain a five-year survival in carcinoma is always a source of gratification. From this viewpoint cancer of the vulva ranks next to cancer of the uterine body in the percentage of successful cases treated. Previous to 1935 there were 108 cases of vulvar cancer in my series. Seven of these refused treatment or went elsewhere. Of the 101 remaining cases, 32 survived a five-year period. Divided according to extent of the disease, these 32 cases were Group I, 9 out of 13 cases (69 per cent); Group II, 14 out of 35 cases (40 per cent); Group III, 9 out of 25 cases (33 per cent); and none of 28 Group IV or V cases.

If we divide these five-year cases according to the method of treatment employed, we find definite evidence of the value of the radical lymph gland resection.

TABLE XI

	CASES	NUMBER SURVIVAL	PERCENTAGE SURVIVAL
Basset and vulvectomy	41	24	58.5
Superficial or incomplete gland removal and vulvectomy	21	6	28.6
Vulvectomy only	12	1	8.2
Radiation treatment	21	1	4.8
Palliative measures (no excision or radiation)	6	0	0.0
Total	101	32	32.0

A review of the literature confirms the statements made in previous papers that treatment by radiologic methods is very unsatisfactory. Stoeckel's compilation gives 12 per cent of five-year cures with radiation alone. Groeger, Reiprich, Ruppert, Stoeckel, and Kehrer give percentages of five-year cures by the use of radical lymph gland excisions with vulvectomy ranging between 36 and 47 per cent. Where only the superficial glands are removed, a compilation from several sources made by me totaling 149 cases showed a 16 per cent five-year survival.

A good illustration of the relative value of radium and surgery in cancer of the vulva was the case of a woman who had an early Group I lesion of the right labia on a leucoplakic basis. She was treated with radium and x-ray by one of the leading radiologists of this country. The tumor completely disappeared, only to re-appear at the original site eight months later. For seven months it continued to grow slowly. Then she came to me and I did a complete vulvectomy. Her age (71 years) and blood pressure contraindicated lymph gland excision. This operation was done two and one-half years ago and at the present time there is no evidence of recurrence.

A further analysis of the five-year survivals following the complete Basset operation reveals some interesting facts. If we divide the cases according to clinical groups, we find that all of the Group I patients remained free of recurrence.

TABLE XII

	CASES	CLINICALLY WELL	PERCENTAGE SURVIVAL
Group I	10	10	100
Group II	20	9	45
Group III	10	5	50
Group IV	1	0	0

It would seem as far as these relatively small figures can be used, that the presence of cancer metastasis was of less significance than the extent of the primary lesion. Data on this point were as shown in Table XIII.

TABLE XIII

	NO. OF CASES	FIVE-YEAR SURVIVALS	PERCENTAGE SURVIVALS
Gland metastasis present	19	10	52.6
Gland metastasis absent	22	14	63.6

Ten-Year Survivals.—With a disease such as carcinoma of the vulva, in which the age incidence is around sixty years, the average expectancy of life would be not over ten years more. Consequently it is not surprising that a considerable number of these women, although cured of their cancer, died of other conditions (pneumonia, heart disease, nephritis) before the ten-year period had been passed. For this reason a calculation of ten-year survivals has less importance than in cancer of the cervix or ovary. Out of 74 treated patients seen over ten years ago, 12 survived a ten-year period (16 per cent). Two of these patients had only a superficial gland dissection, with a ten-year survival of 12 per cent in the 17 cases in this group. Out of 24 patients subjected to a complete Basset operation over ten years ago 16 survived the five-year period and ten survived the ten-year period (41 per cent). Of the six who died in this second five-year interval, four had recurrences of the vulvar lesion, one died of a new cancer originating in the breast and one died of an acute influenzal pneumonia. Of the 10 patients who survived the ten-year period, we find only 6 still living today. The four deaths in this group were due to: (1) late local recurrence of the disease; (2) a new cancer of the cervix appearing fourteen years after cure of the vulvar lesion; (3) apoplexy in a woman 87 years of age; (4) senility in a woman 85 years of age. The two patients who have survived for the longest period of time were operated upon 16 and 17 years ago, respectively.

CONCLUSIONS

1. Early recognition and prompt adequate treatment are extremely rare in cancer of the vulva. In spite of this the disease, because of its relatively slow growth, offers a reasonably good prognosis.

2. Prevention of carcinoma of the vulva by early excision of the leucoplakic vulva should materially lower the incidence of the disease.

3. Radiologic treatment of the disease gives disappointing results, and is usually attended by painful burns.

4. The complete modified Basset operation gives splendid results in patients with operable lesions (Clinical Groups I-III) who are under 65 years of age. In older patients only those in better than average physical condition with relatively early lesions should be subjected to this procedure.

5. Approximately two-thirds of the cases of cancer of the vulva are still operable at the first examination. In those in whom a Basset operation is done we can expect a five-year survival in about three out of five (58.5 per cent), even though two out of five (41 per cent) already show evidence of lymph gland metastasis.

3720 WASHINGTON BOULEVARD

DISCUSSION

DR. JOHN R. FRASER, MONTREAL, CANADA.—It is encouraging for me to know that this disease which we have always regarded as being most unsatisfactory from a therapeutic point of view, will under certain circumstances yield such excellent results after five years. It is true that the bulk of these cancers are skin cancers. The unsatisfactory ones, of course, are the vestibular lesions, the periurethral lesions, and the more rare Bartholin gland lesions.

Seventy per cent of these patients Dr. Taussig has been able to treat in a surgical manner. There remain 30 per cent who are beyond the scope of surgery. That is the first discouraging fact. The second is that these lesions occur in women even in the later decades where other disabling conditions make them uncertain surgical risks.

Dr. Taussig brought out some very important points. First, leucoplakia is found in a large percentage of these women and is a disease which can be cured surgically. Second in cancer of the vulva there is a high incidence of metastases which are not clinically discernible. The latter is an important point in determining our procedure in the treatment of these lesions.

In our small group we have had since 1926 just 30 cases. Twenty-one of these are suitable for discussion from the standpoint of a five-year cure. Of these 21 cases, we saved 5, one being cured by radium, 2 by the use of electric cautery and surgery, and 2 by surgery alone. This simply shows that the best treatment so far as we have found is excision of the local lesion and a widespread removal of the gland-bearing tissue when the condition of the patient will stand it.

DR. KARL M. WILSON, ROCHESTER, N. Y.—I would like to present two rather interesting examples of rare vulval tumors which have been under my observation and which are of the melanotic type. The first case was in a far-advanced stage and the patient was dead two months after she came under observation.

The second patient, on the other hand, had had a melanotic tumor present two months before observation. She was 62 years of age and she was a diabetic and also an arteriosclerotic, therefore a rather poor surgical risk. We did a vulvectomy first and later, a resection of the glands on both sides. Seven years after operation she was in excellent condition. My experience with melanotic tumors is limited to those two cases. Call it a 50 per cent survival if you will.

DR. BENJAMIN P. WATSON, NEW YORK, N.Y.—It has been my experience that one of the early symptoms of cancer of the vulva is pain in the ulcerated lesion, and also tenderness in handling that lesion. It has in fact been my teaching to the students that whenever they find any ulcerative condition of the vulva which is painful or tender, they should immediately suspect carcinoma.

DR. TAUSSIG (closing).—Bartholin gland tumors, in my experience, are almost as favorable as the epidermal type. We have 3 patients who have passed the five-year period in our series.

As to the operative deaths, the immediate shock from the extent of the operation has not been a factor in our primary mortality. None of the five patients that died as a result of the Basset operation died earlier than the sixth day. Of course, there was toxic absorption and occasional infection due to the size of the wound, but the immediate operative mortality was nil.

I do not think that it is quite correct to say that vulvar cancer is comparable to cervix cancer in regard to its five-year cure rate. Thirty-two per cent in our total series is not a fair basis for comparison, since many of these cases in the earlier years were insufficiently treated. The important thing is that in the Basset type of operative treatment, which is utilizable in 70 per cent of all cases, we can cure approximately three-fifths of the cases, which is certainly far better than we can expect in cervix cancer.

Three patients with melanoma were included in this series and they all died. I have one patient with melanoma of the mons veneris who remained well for seven years.

As to the symptom of pain in the vulva, I should have included that under the heading of ulcer as a symptom. All ulcers about the external genitals are painful, and perhaps soreness of the vulvar region might have been a better term to apply than ulceration.

As to the use of x-ray, we have found no advantage in that procedure and would rather discount the employment of such measures in addition to surgery, in view of our excellent results without x-ray.

CARCINOMA OF THE CERVIX AFTER SUPRAVAGINAL HYSTERECTOMY*

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THE material for this study was obtained from the records of sixty-seven patients in whom carcinoma of the cervix was recognized at some time after supravaginal hysterectomy had been performed for various indications. Forty-three of these cases, all white women, were observed on the Gynecologic Service of the University Hospital. The remaining twenty-four patients, fifteen of them white and nine colored, were treated in the Radiologic Department of the Philadelphia General Hospital.

From 1913 to 1939 inclusive, 910 patients with carcinoma of the cervix were admitted to the Gynecologic Service of the University Hospital. In this case series, the cancer was recognized some time after supravaginal hysterectomy had been performed in 43 patients, an incidence of 4.7 per cent. In the second series, which comprised the 1,117 patients who had been admitted to Philadelphia General Hospital since the establishment of its Radiologic Department, in 1922, supravaginal hysterectomy had been carried out prior to the diagnosis of cancer in 24 cases, an incidence of 2.15 per cent.

Age.—The youngest of these patients was thirty-two years of age, and seventy-six was the age of the oldest in the series (Table I). The age distribution of the entire group varies little from that observed in patients with "cervix" cancer when the fundus of the uterus is present.

Previous Operation.—The most frequent indication for hysterectomy was fibromyoma uteri (Table II). Pelvic inflammatory disease was the indication second in order of frequency. Both of the patients who had been hysterectomized for carcinoma of the fundus had epidermoid carcinomas of the retained cervices. Three instances of hysterectomy for carcinoma of the fundus, followed by adenocarcinoma of the stump, were not included in this study.

Initial Symptom.—The initial symptom most commonly elicited was bleeding (Table III). This was reported by 51 of our patients, or 76 per cent. Rarer first symptoms were loss of weight, irritating discharge, and pain. The single instance in which no initial symptom was reported was a case discovered at the time of the hysterectomy, by biopsy of a clinically undiagnosable lesion of the cervix. Prompt radiologic treatment was given and this patient is still living and well after more than five years.

Degree of Involvement.—To avoid minute subdivisions, lesions corresponding to Stages I and II, Schmitz's classification, were grouped together (Table IV). There was little difference in the end results obtained in Stages I, II, and III. This may have been due to the small number of cases studied, but we are of the opinion that it indicates greater difficulty in grading carcinoma of the cervix after the fundus has been removed than when no uterine trauma has preceded. No patients whose disease was in the fourth stage survived five years.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, Seigniory Club, June 17 to 19, 1940.

TABLE I. AGE OF PATIENTS

AGE	NO. OF CASES
30-39 years	10
40-49 years	30
50-59 years	20
60-69 years	6
Over 70 years	1
Total	67

45 per cent in fifth decade. 74 per cent in fifth and sixth decades.

TABLE II. INDICATION FOR HYSTERECTOMY

DISEASE	NO. OF CASES
Fibromyoma uteri	39
Pelvic inflammatory disease	11
Myoma and pelvic inflammatory disease	3
Carcinoma of the fundus	2
Benign hemorrhage	1
Not stated	11
Total	67

Two patients hysterectomized for carcinoma of fundus later had epidermoid carcinoma of cervix.

TABLE III. INITIAL SYMPTOM REPORTED

SYMPTOM	NO. OF CASES
Bleeding	51
Loss of weight	4
Irritating discharge	3
Pain	3
No clear record	5
No symptom	1
Total	67

Case without symptoms was discovered unexpectedly by routine biopsy.

TABLE IV. DEGREE OF INVOLVEMENT AND SALVAGE

STAGE	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
I and II	4	3	4	11
III	10	13	3	26
IV	0	28	2	30
Total	14	44	9	67

Results in Stages I, II, and III were similar.

*Alive, less than five years after treatment.

Pathologic Diagnosis.—Squamous cell carcinoma was the type of tumor found in 78.5 per cent of the cases, in which histologic examinations of the tumors were made (Table V). Thirteen patients for whom no pathologic diagnoses were recorded were included in the series. None of these lived five years after treatment and the progressive course of their disease attested the accuracy of the clinical diagnoses. The salvage of the patients with squamous cell carcinoma was three times that of those who had adenocarcinoma of the stump.

Treatment.—Three of the women in this series were unsuitable for any treatment because of the widespread invasion of the cancer and their poor physical condition. The remainder were treated radiologically (Tables VI and VII). Most of them received contact radium, or its emanations, into the canal or across the split stump. Some of these were also given external irradiation by means of high voltage (200

TABLE V. HISTOLOGIC DIAGNOSES

TYPE	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Squamous cell carcinoma	13	23	7	43
Adenocarcinoma	1	8	2	11
Not recorded	0	13	0	13
Total	14	44	9	67

Cases without histologic diagnoses are all dead.

*Alive, less than five years after treatment.

TABLE VI. TREATMENT AND RESULTS (UNIVERSITY HOSPITAL)

NO. CASES	TREATMENT	5-YEAR SALVAGE
2	600 mg. hr. or less	0
7	1,000-2,000 mg. hr.	2
21	2,400-3,600 mg. hr.	5
6	Over 4,000 mg. hr.	3
2	1 Series (high voltage therapy)	0
1	Untreated	0
4	Alive, less than 5 yr.	
43	Totals	10

Best results were secured with moderately high dosages.

TABLE VII. TREATMENT AND RESULTS (PHILADELPHIA GENERAL HOSPITAL)

NO. OF CASES	TREATMENT	5-YEAR SALVAGE
2	Less than 1,000 mc. hr.	0
4	3,500 mc. hr. 2 Series H. V. T.	0
8	5,000 mc. hr. 2 Series H. V. T.	4
2	3 Series H. V. T.	0
3	Untreated	0
5	Alive, less than 5 years	
24	Totals	4

Best results were secured with moderately high dosages.

kv.) roentgen therapy, and others had external irradiation without radium therapy. The latter were, as a rule, the more advanced cases. In recent years, vaginal applications of radium or radon were given at a distance of 1 cm. with filters equivalent to 2 mm. platinum. The best results were secured in those cases whose radium dosage was from 2,400 mg. hr. to 5,000 mg. hr.

Von Graef[1] suggested that carcinoma of the cervix discovered within one year after subtotal hysterectomy should be regarded as having been present at the time of the operation. Nuttall and Todd[2] proposed a two-year criterion. Considerable evidence has been presented[3, 4] that the life history of "cervix" cancer may span a period of eight or more years, and we believe that the three-year interval suggested by Healy and Arneson[5] is a fair index of the development of the tumor after the hysterectomy. On this basis (Table VIII), it is probable that 29 (43 per cent) of our patients treated more than five years ago, had carcinomas of the cervix when the supravaginal hysterectomies were performed. In two of this group, biopsies from suspicious cervices, secured at the time of the hysterectomies, enabled early diagnoses and treatment. These are the only cases discovered less than three years after the hysterectomy who survived for five years. If none but the patients diagnosed three or more years after hysterectomy were considered, the five-year salvage would be 41.4 per cent.

TABLE VIII. ELAPSED TIME BETWEEN HYSTERECTOMY AND RECOGNITION

YEARS	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Less than 3	2†	27	3	32
3-10	5	5	3	13
10 plus	7	12	3	22
Total	14	44	9	67

Poor salvage under three years. Fair salvage over ten years. Best salvage three to ten years.

*Alive, less than five years after treatment.
†Diagnosed by biopsy at time of hysterectomy.

In only 22 patients (33 per cent) was the disease recognized within six months of the appearance of the first symptom (Table IX). Eight of these (40 per cent) survived for five or more years, whereas the salvage among those treated one year or more after the first symptom was only 4.5 per cent.

TABLE IX. DURATION OF SYMPTOMS BEFORE RECOGNITION

TIME	NO. CASES SALVAGED	NO. PATIENTS DEAD	NO. PATIENTS LIVING*	TOTAL
Less than 6 months	8	12	2	22
6-12 months	4	6	2	12
1 year or more	1	21	5	27
Not stated	1	5	0	6
Total	14	44	9	67

Best results secured when treatment was given early.

*Living, less than five years after treatment.

It has been pointed out[6, 7] that vesicovaginal fistulas are more common complications of carcinoma of the cervix when the fundus of the uterus has been removed. Their relatively frequent occurrence under these circumstances has been attributed to the destructive effects of the radium radiations to the bladder, mobilized into closer relationship with the stump of the cervix during hysterectomy. There were nine vesicovaginal fistulas in our combined series, an incidence of 13 per cent. In the group of cases from Philadelphia General Hospital, there were 6 vesicovaginal fistulas; an incidence of 25 per cent. Two of these patients also had rectovaginal fistulas. There were no fistulas in any of the patients who survived the five-year limit. Two of the 9 fistulas occurred in women who received no treatment at all. One of the patients was given only high voltage roentgen therapy. It would seem highly probable, therefore, that, as in carcinoma of the cervix in general, fistulas are due to the invasion of the cancer in cervical carcinoma after supravaginal hysterectomy rather than to the effects of the treatment. Table X shows the fistulas discovered among 1,117 carcinoma of the cervix patients from

TABLE X. FISTULAS OCCURRING IN 1,117 CASES OF CARCINOMA OF THE CERVIX, INCLUDING STUMP CARCINOMAS. GREATEST INCIDENCE WAS IN LATTER GROUP. UNTREATED CASES RANKED SECOND. (PHILADELPHIA GENERAL HOSPITAL.)

FISTULAS	NO. TREATED	NO. UNTREATED	NO. "STUMP CARCINOMAS"
	869	248	24
Vesicovaginal	34	49	4
Rectovaginal	39	0	2
Vesicovaginal and Rectovaginal	13	16	2
Total	86 (10%)	65 (26%)	8 (33%)

the same clinic. Fistulas occurred three times as often in the untreated and "stump" cases as in the large group of treated patients with the fundus present.

TABLE XI. COMPARATIVE SALVAGE

	CASES IN SERIES	SALVAGE CARCINOMA CERVIX	SALVAGE "STUMP CARCINOMA"
Univ. Hospital	910	18%*	26%
Phila. General Hospital	1117†	5.8%	21%

Treatment of carcinoma of the cervix after supravaginal hysterectomy was essentially the same as for general carcinoma of the cervix in each hospital.

*Computed to 1931 inclusive.

†248 patients were not treated.

RESULTS

In Table XI one sees that the results secured by treatment of carcinoma of the stump in each hospital series were better than those following identical treatment, in the same hospital, of carcinoma of the cervix, regardless of whether or not the fundus was present. If only the cases discovered three or more years after subtotal hysterectomy were considered, the salvage would amount to 41.4 per cent. Furthermore, the salvage was 40 per cent in the group who received treatment within six months of the appearance of the first symptom. The very low salvage rate in the Philadelphia General Hospital series is attributable at least in part, to the advanced stage of the disease when most of the patients were admitted for treatment. Two hundred and forty-eight of the 1,117 patients seen in that hospital were unsuitable for any sort of treatment at the time of admission.

Post-mortem examinations were performed on 3 of the 10 patients who died in the Philadelphia General Hospital series. In one there were metastases to the liver and lungs. A second had metastatic nodules in the lung, and in the third, there was no evidence of extension of the disease beyond the pelvis.

TABLE XII. COLLECTED STATISTICS

	NO. CA. CERVIX	SALVAGE CARCINOMA CERVIX PER CENT	INCIDENCE "STUMP CARCINOMA" PER CENT	SALVAGE "STUMP CARCINOMA" PER CENT
Ward and Sackett[8]	752	28.5	7.4	44.2
Scheffey[9]	273	20.5	3.66	42.8
University and Philadelphia General	1,764	10.4	3.9	24.0
Healy and Arneson[5]	2,600	24.0	2.6	14.0
Von Graef[1]	4,269		4.1	9.0*
Meigs[10]	1,218		4.7	
Smith and Bartlett[11]	673		4.0	

In four clinics the five year salvage is twice as great in the "Stump" Carcinomas as in Carcinoma of the Cervix in general.

*Pertains only to 331 patients treated by irradiation.

Collected statistics are shown in Table XII. In the combined cases of Ward and Sackett,[8] Scheffey,[9] and in this series, the salvage among the stump cancers was approximately twice that achieved with general carcinoma of the cervix in the same clinics. Healy and Arneson attribute their lower salvage rate to inadequate irradiation. They observe, however, that results were as good in patients whose lesions were advanced as with tumors of the same stage when the uterus was present. Their dosage for stump cancers was considerably lower than that used in the first four clinics in the table.

DISCUSSION

Distinctions are invariably made between the behavior of carcinoma of the cervix when the fundus is present and the same disease when the body of the uterus has been removed. "Stump cancer" is alleged

to be more refractory to treatment.[5, 12] This has been attributed to difficulty in making proper application of radium in sufficient dosage when the uterine canal has been shortened by hysterectomy. Interference with circulation to the cervix due to contraction of scar tissue in the parametria, following the trauma of supravaginal hysterectomy, has been said to diminish the chance for curing the tumor of the stump.

In the course of our routine follow-up observations at the University and Philadelphia General Hospitals, we secured the impression that carcinoma of the cervix varied little in its characteristics whether or not the fundus was present when the disease was discovered. The data presented above show nothing peculiar about "stump" carcinoma with regard to age, initial symptoms, or histologic characteristics, as compared with carcinoma of cervices from which the fundus has not been removed.

Our results as well as those from several other clinics indicate that the disease is just as amenable to treatment as when the fundus is present. In some instances, the results are distinctly better in "stump" carcinoma. It would seem logical to expect that after subtotal hysterectomy contractures of fibrous tissue in the parametrial regions might tend to keep the disease localized to the cervix for a relatively longer period of time. By compressing the blood vessels and lymphatics in these areas, the diminished circulation to the tumor might result in slower growth, and interference with lymphatic drainage should retard permeations. Castration, a procedure often performed with hysterectomy, has been recommended as a factor retarding the growth of carcinoma in other situations. There is no evidence to the contrary as far as carcinoma of the cervix is concerned. It is usually observed, furthermore, that carcinoma of the cervix is more rapidly invasive in patients of the younger age groups. The senilizing effects of castration should, therefore, be a favorable influence upon the course of the disease.

Before high voltage roentgen irradiations were available, it required considerable ingenuity to subject the carcinoma, situated in a short stump of the cervix, to cross-fire from the positions necessary to attain adequate dosage. This difficulty was overcome in many of the cases in our series by splitting the cervix transversely with a cautery to a depth equal to about one-half of the length of the stump. The radium tube was then placed crosswise within the lips of the split cervix. By augmenting the radium application with external irradiations, most of these tumors can be safely and adequately irradiated. Per-vaginal high voltage x-ray therapy was employed in one of our recent cases, as well as for more than 50 patients with ordinary cervical cancer. This form of irradiation seems peculiarly adapted for safe and thorough irradiation of cancerous cervices after the fundus has been removed.

From the results secured in those "stump" cancers recognized three years after subtotal hysterectomy, it is perhaps fair to infer that the cervical carcinoma patient had a better chance of cure if the uterus had been removed before the cancer was acquired. The disastrous outcome of our patients whose carcinoma was discovered less than three years after supravaginal hysterectomy would indicate that removal of the fundus, after the carcinoma has been established in the cervix, is of no benefit.

Our findings are in accord with the opinion of Phaneuf that vesicovaginal fistulas are more frequently seen in carcinoma of the cervix when the fundus of the uterus has been removed than when it is retained. We submit, however, that this should not be attributed entirely to the effects of radiation but must in many instances be blamed on persistent invasion of the vesicovaginal septum by the carcinoma, in spite of the treatment administered.

SUMMARY

1. Carcinoma of the cervix after supravaginal hysterectomy behaves similarly to the same disease when the fundus is retained.

2. Its response to treatment is no worse than that of "cervix" cancer in general, and in some clinics is better.

3. Approximately 40 per cent of "stump" cancers recognized three years after subtotal hysterectomy, or within six months of the appearance of the first symptoms, were living and well five years after treatment.

4. Subtotal hysterectomy appears to improve the chance of cure if performed before carcinoma of the cervix has been acquired.

5. The probable development of vesicovaginal fistulas is greater than when the fundus is present. Fistulas are more often due to the disease than the result of treatment.

6. Meticulous examination of the cervix should be made a part of every gynecologic examination. Areas which are abnormal should be removed for histologic study. These principles are no less important when removal of the fundus is contemplated.

7. Complete hysterectomy is an excellent manner of dealing with disease of the cervix when the fundus is to be removed. However, in the hands of those whose experience is limited, supravaginal hysterectomy, combined with trachelectomy, is satisfactory and less hazardous.

REFERENCES

(1) *Von Graef, E.:* Am. J. Obst. & Gynec. **28:** 18, 1934. (2) *Nuttall, J. R., and Todd, T. F.:* J. Obst. & Gynaec. Brit. Emp. **42:** 860, 1935. (3) *Hunter, O. B.:* South. M. J. **32:** 179, 1938. (4) *Stevenson, Charles S., and Scipiades, Elmer, Jr.:* Surg. Gynec. Obst. **66:** 822, 1938. (5) *Healy, W. P., and Arneson, A. N.:* Am. J. Obst. & Gynec. **29:** 370, 1935. (6) *Phaneuf, L. E.:* Am. J. Surg. **29:** 479, 1935. (7) *Morton, D. G.:* Surg. Gynec. Obst. (Int. Abst. Surg.) **65:** 177, 1937. (8) *Ward, George Gray, and Sackett, Nelson B.:* J. A. M. A. **110:** 323, 1938. (9) *Scheffey, Lewis C.:* J. A. M. A. **107:** 837, 1936. (10) *Meigs, J. V.:* Am. J. Obst. & Gynec. **31:** 358, 1936. (11) *Bartlett, M. K., and Smith, Geo. Van S.:* Surg. Gynec. Obst. **52:** 249, 1931. (12) *Tagliaferro, P.:* Ann. di ostet. e ginec. **57:** 1089, 1935.

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DISCUSSION

DR LOUIS E. PHANEUF, Boston, Mass.—I have recently investigated 15,000 personal case histories and found stump carcinoma eight times, or once in 1,875 cases. In all instances, the supravaginal hysterectomy had been performed by other surgeons.

Eight patients were treated with radium, the largest dose being 6,100 mg. hr., and the smallest 2,400 mg. hr. In addition, 7 of the patients had high voltage x-ray therapy.

In three women, the carcinoma existed in the cervix at the time of the subtotal hysterectomy. One is alive and well eleven and one-half years after the initial treatment, while the other two died two and one-fourth years and five months, respectively, afterward.

In the 5 remaining patients, the carcinoma developed in periods ranging from a short time to thirty years after the supracervical hysterectomy. Two are now alive and free from recurrence, five years and three months, and three years and five months, respectively, after treatment. Three have died, surviving the initial treatment three years and eleven months, one year, and seven months, respectively.

From the standpoint of prophylaxis, all these cases had had an indication for hysterectomy, and the total operation would have prevented the malignant lesion. This may serve as an argument in favor of the more common employment of panhysterectomy for benign lesions of the uterus.

DR. GEORGE GRAY WARD, New York, N. Y.—The last report from the Woman's Hospital on carcinoma of the stump was given about three years ago when Dr. Sackett reported an incidence of 7.2 per cent of carcinoma of the cervix after supravaginal hysterectomy. This report included all cases even though they occurred within the first year following the hysterectomy. I have recently had the records gone over from May, 1919, to May, 1940, and tabulated as follows:

Table I shows the survival rate. In 852 cases of cervical carcinoma seen during that period, 57 were stump cases, or 6.7 per cent. In 49 observed during a five-year period, 21 were living, or an absolute survival rate of 42.8 per cent. In 20 observed during a ten-year period, 10 were living, or an absolute survival rate of 50 per cent. One case of the 57 was not treated.

Table II shows the number of complications after irradiation. Three patients developed rectovaginal fistula, and 2 vesicovaginal fistula. With 5 in all the incidence of fistula was one and one-half times as high in stump cases as in the usual cervical cancers. The average duration of life in recurrent cases following treatment was fifteen months. Two patients died after two and three years from other diseases than carcinoma.

Table III shows the time between hysterectomy and postoperative radiation. Of the 57 cases, 16 developed within the first year after the hysterectomy. Of these first-year cases, 5 survived five years and 3 survived ten years. Undoubtedly in some of these patients the disease was present at the time of the hysterectomy. In 41 the disease developed more than one year after operation. Of these 16 survived five years, or 32.7 per cent of 49 observed, and 7 survived ten years, or 35 per cent of 20 observed. There were 28 cases arising three years following operation, or 3.28 per cent, which Dr. Behney mentioned as a better time limit to be sure that carcinoma was not present at the time of the hysterectomy.

Table IV gives both the Schmitz and the League of Nations classification of the extent of the carcinoma. In the 57 cases seen, 13 could be classified as early and 44 as advanced. Of the 13 patients with early cases 8 survived five years and 4, ten years. Of the 44 late cases, 13 patients survived five years and 6 ten years.

Table V shows that 45 cases were squamous cell, of which 20 survived five years, or 44 per cent, and 9 survived ten years, or 20 per cent. There were 10 cases of adenocarcinoma, 2 surviving five years, or 20 per cent, and 1 ten years, or 10 per cent. In 2 cases the type of cell was undefined.

Table VI shows the average dose of radium applied which was about 3,200 mg. hr. of element. High voltage x-ray follows or precedes, preferably given according to the Coutard technique. Before 1930 we had no high voltage x-ray. Thirty-six patients were treated with radium alone of which 29 were under treatment before 1930. Sixteen of these survived five years, and 9 survived ten years. Twenty patients were treated with both radium and x-ray, of which 5 survived five years, and 1 survived ten years. One patient was not treated.

I am in agreement with Dr. Behney in what he says about the behavior of these cases being in general similar to those in which there has been no hysterectomy. On the other hand, I believe that there is definitely more danger of fistula, owing to the proximity of the bladder.

I feel very definitely that the complete operation, a panhysterectomy, is to be preferred whenever it is possible to do it without additional danger to the patient.

DR. WILLIAM C. DANFORTH, Evanston, Ill.—It seems to me that there is a very strong argument for a wider use of the total operation which after all is the most effective type of prophylaxis against cervical cancer. Possibly the recommendation of this generally may not be wise, but in the hands of competent operators, I venture to say that the difference in mortality is *nil*.

In my own group within the past five or six years, there have been about 500 cases in which total abdominal hysterectomy has been carried out, either vaginally or abdominally, and we have not had any difference in mortality at all.

DR. FRANK A. PEMBERTON, Boston, Mass.—Our results at the Free Hospital for Women are about the same as Dr. Behney's. We have had 40 stump carcinomas in 780 cases of cancer of the cervix, a 6 per cent incidence. It is also of note that 10 (25 per cent) of our group occurred in nulliparas. Hence the fact that a woman has not borne children is not an indication for leaving the cervix in when deciding on whether or not to do a complete or supravaginal hysterectomy. The condition of the cervix is what counts.

The five-year salvage in this group was 16 patients, 40 per cent, about the same as Dr. Behney and Dr. Ward reported. Our series of cancers of the cervical stump extends over the period from 1909 to 1933. We treated 274 cases of cancer of the cervix between 1929 and 1933, inclusive, and have a five-year salvage of 38 per cent, about the same as for the salvage of stump cancer over the whole period.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Four years ago, at the Kansas City meeting of the A. M. A., I presented a similar study, a part of which I have brought up to date for this meeting, and offer as a contribution to this problem.

Table I shows the incidence of carcinoma of the cervical stump as seen on the Gynecologic Service at Jefferson Medical College Hospital from 1921 to 1940. The figure of 4.8 per cent approximates Dr. Behney's University of Pennsylvania figure. Of the entire series now presented, only one could be classified as a Group I (Schmitz) lesion. Fourteen were in Group III, 1 in Group IV, and 2 in Group V. Only 2 were adenocarcinomas and neither patient lived for very long. The youngest patient was 30; the eldest 72. About one-fourth (27.7 per cent) were under 40.

Table II depicts the comparative salvage (relative) between cervical carcinoma and cervical stump carcinoma. In our previous study, we reported a salvage of 42.8 per cent; today the figure is 41.6 per cent, a far better figure than we obtained in the treatment of carcinoma of the cervix in general. This is in accord with Dr. Behney's findings. The treatment has been predominantly with radium, and with a relatively high dosage, 3,000 to 4,500 mg. hr., with additional x-ray therapy in only a few instances.

Table III shows the salvage in relation to the lapse of time after the supravaginal hysterectomy. Since all of the patients successfully salvaged, with one ex-

TABLE I. INCIDENCE OF CARCINOMA OF CERVICAL STUMP

Carcinoma of cervix	369 patients
Carcinoma of cervical stump	18 patients
Incidence	4.8 per cent

TABLE II. COMPARATIVE FIVE-YEAR SALVAGE (RELATIVE) 1921 TO 1935

5-YEAR SALVAGE	CARCINOMA CERVIX PATIENTS TREATED—259	CARCINOMA CERVICAL STUMP PATIENTS TREATED—12
Including cancer death	23.5% (61 patients)	58.3% (7 patients)
Excluding cancer deaths	17.7% (46 patients)	
Present-day Salvage	15.8% (41 patients alive 5 to 19 years)	41.6% (5 patients alive 6 to 12 years)

ception, showed relatively advanced lesions, it would seem that carcinoma of the cervical stump has been remarkably amenable to radiation therapy, irrespective of the lapse of time after supravaginal hysterectomy.

TABLE III. SALVAGE IN RELATION TO LAPSE OF TIME AFTER SUPRAVAGINAL HYSTERECTOMY

YEARS AFTER	NUMBER PATIENTS	5-YEAR SALVAGE (CANCER DEATHS)	PRESENT-DAY SALVAGE
1 to 3	5	0	2 (8, 12 yr.)
3 to 10	6	2 (6, 9 yr.)	1 (12 yr.)
10 to 25	7	0	5 (½, 1, 3, 6, 10 yr.)

DR. LILIAN K. P. FARRAR, New York, N. Y.—Why comfort oneself with the thought that a carcinoma of the cervix can be treated just as well after the fundus is taken out? Take out that cervix with the fundus and the patient will not have the carcinoma.

Dr. Pemberton demonstrated last year the pathologic condition of the cervix in a series of total hysterectomies. Dr. Danforth has told you that the same mortality is possible after a total as after a supravaginal hysterectomy. Yet we continue to say that total hysterectomy should not be generally advised and that it is not for the average surgeon. I earnestly urge this Society not to be satisfied with merely devising methods for the inadequately trained surgeon, but to raise the standards of pelvic surgery and give better protection to American women.

DR. JAMES C. MASSON, Rochester, Minn.—In the Mayo Clinic, at the last compilation, we had found 164 and, I am sure by now, there are 170 cases of carcinoma in the cervical stump. We also have seen about 500 patients who had cervicitis with leucorrhea which was sufficient to require treatment. In many of these cases there was no history of leucorrhea before the body of the uterus had been removed.

I agree with what Dr. Farrar has said. Why should the members of this Society, who specialize in gynecology, advise subtotal operation as often as they do? If the complete operation can be done as safely as the subtotal, and I believe it can, why should we do so often the subtotal operation?

DR. WILLIAM A. SCOTT, Toronto, Canada.—Although it is my belief that total hysterectomy should play a larger part in the operative procedure of the skilled gynecologist, I would like to point out a fallacy in the present argument. It is stated that cases in which carcinoma of the stump develops within three or five years should be looked upon as having been present at the time of operation. Nevertheless, in Dr. Farrar's paper last year, there were 460 cases of total hysterectomy for benign conditions, and in none of these was an unsuspected carcinoma discovered after careful pathologic examination of the cervix. In the discussion of that paper, I noted only one instance in my series where such unsuspected carcinoma was found, and Dr. Pemberton found no example in 100 consecutive cases on whom he had operated. It would appear, therefore, that in these series at least, unsuspected cancer at the time of operation was of no significance, and had subtotal hysterectomy been done, subsequent cancer of the stump, had it developed, would have been a new disease.

DR. HERMANN J. BOLDT, White Plains, N. Y.—I have had a fairly large experience of something over fifty years and in my opinion the important thing to remember is to see what the condition of the cervix is at the time of operation. Invariably a complete hysterectomy should be done if an eroded cervix exists.

DR. BEHNEY (closing).—I should like to clarify my attitude toward total and subtotal hysterectomy. Statistics (Table I) show an incidence of carcinoma of the stump varying from 0.1 to 6 per cent of the subtotal hysterectomies performed. The number of cases considered is not stated in all instances, but Sejourinet has reported over 5,000 hysterectomies with 1.9 per cent of carcinoma of the cervix following, and in the large series reviewed by Hennington, the incidence was 0.57

TABLE I. CARCINOMA OF THE CERVICAL STUMP
COLLECTED STATISTICS

AUTHOR	NO. OF HYSTER-ECTOMIES	INCIDENCE STUMP CARCINOMA	AUTHOR	NO. OF HYSTER-ECTOMIES	INCIDENCE STUMP CARCINOMA
Lincoln		6.5%	Von Graef	4,269	0.62%
Lahey	900	2.0%	Hennington	18,712	0.57%
Sejourinet	5,712	1.9%	Albrecht		0.40%
White		1.8%	Fahndrich		0.40%
Richardson		1.0%	Meigs		0.13%
Scheffey	554	0.9%			

per cent. Dr. Phaneuf has just cited 15,000 cases of supravaginal hysterectomy with 7 instances of stump carcinoma following. The experiences of Ward, Scheffey, and ourselves indicate the curability of stump cancer to be about 40 per cent. It would seem, therefore, that the danger to the life of the patient from permitting the stump of the cervix to remain after hysterectomy is quite small.

In our own practice we perform total hysterectomy whenever the cervix is diseased, provided that there are no technical difficulties connected with this procedure which might increase the operative risk. Our policy in this regard is very little influenced by our fear of the development of carcinoma in the retained stump. We prefer total hysterectomy in such cases, because the removal of a diseased cervix disposes of a focus of infection, reduces morbidity, and greatly enhances the patient's chances for future good health.

It should also be emphasized that total hysterectomy is not the final solution of the problem of carcinoma as a later complication. Sejourinet, Lahey, and others have cited cases in which carcinoma of the vault of the vagina followed total hysterectomy. In our series at Philadelphia General Hospital, there were three patients who had carcinoma of the vault of the vagina following total hysterectomy and were, therefore, not included in this series.

The cases presented in this study were of patients operated upon by surgeons in the Philadelphia district. Some of them were by experienced gynecologists, a few by members of this Society. Yet there were a number of instances where carcinoma of the stump occurred within a comparatively short time after the supravaginal hysterectomy, and we are obliged to conclude that even experienced gynecologists at times perform supravaginal hysterectomy without careful study of the cervix. This occurs most frequently in instances where large tumors dominate the picture, and apparently insignificant disease of the cervix is disregarded. So long as this occurs, and so long as general surgeons, who do not enjoy the opportunity of a great gynecologic experience, must perform the gynecologic surgery in small hospitals, it seems entirely proper to recommend to those who consider themselves incapable of performing total hysterectomy, the alternative of supravaginal hysterectomy with amputation of the cervix and careful study of the removed tissues.

CARCINOMA OF THE BODY OF THE UTERUS*

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THE complacency which characterizes treatment of corpus carcinoma probably has a twofold origin, (1) the fallacious belief that the prognosis is invariably good, and (2) the tendency to compare results with other less amenable carcinomas. Survival studies have shown that the prognosis is not always good, and further that we have not yet taken full advantage of the remedial measures at our command.

This study is based on 183 patients with microscopically verified carcinoma of the body of the uterus seen in the Gynecological Tumor Conference at the University of Michigan Hospital since April, 1931. It also includes 3 patients seen in 1930. All patients have been followed since their original examination, there are no untraced cases. While we are primarily interested in the results of therapy considerable data of general interest have been tabulated.

GENERAL STATISTICS

Age.—The average age for the entire group was fifty-four years.

Race.—Among the 183 patients, only one was colored. The remainder were white.

Geographic Distribution.—All but 8 patients in our series came from the State of Michigan. They constitute a large number of the more advanced cases coming, as they do, from the poorer economic group.

Marital status.—One hundred and seventy-seven patients were married, six were single. Of the 183, 135 (73 per cent) had been pregnant, 48, or 27 per cent, had never conceived. The average number of children among the former was 3.1. Only 30 had 5 or more children.

Symptoms.—The chief symptoms noted were as indicated in Table I.

TABLE I. SYMPTOMS

SYMPTOM	NUMBER	PER CENT
No symptoms	3	1.6
Bleeding or spotting	160	88.0
Nonbloody discharge	8	4.3
Tumor mass	6	3.2
Pelvic pain	6	3.2
Total	183	100.3

Duration of Symptoms.—The duration of symptoms is an indication of time wasted, chiefly by the patient. Information on this point is presented in Table II.

Since time wasted by patients prior to seeking advice is of tremendous importance, further comment regarding this observation is desirable. *Among 147 patients with abnormal bleeding, there existed an average time waste of 7.1 months prior to the patient's seeking advice concerning the cause of the bleeding. The aver-*

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

age time waste from the first medical examination to the institution of treatment was approximately four months, a total time waste of approximately eleven months.

TABLE II. DURATION OF SYMPTOMS

DURATION OF SYMPTOMS	NUMBER	PER CENT
No symptoms	3	1.6
No delay, treatment sought immediately	3	1.6
Delay of one month or less	40	22.4
Delay of 2 to 3 months	16	8.7
Delay of 3 to 6 months	35	19.0
Delay of 6 to 12 months	30	16.3
Delay of 12 to 18 months	13	7.1
Delay of more than 18 months	43	23.5
Total	183	100.2

TABLE III. TIME WASTE PRIOR TO SEEKING ADVICE AND TREATMENT

AVERAGE TIME WASTE	MONTHS	WEEKS	DAYS
From onset of symptoms to diagnosis	7.1	28	196
From diagnosis to beginning of treatment	4.0	16	112
Total	11.1	44	308

TABLE IV. COMPARATIVE STUDY OF TIME WASTE AMONG PATIENTS WITH CORPUS CARCINOMA

REPORTED BY	AVERAGE TIME WASTE—ONSET OF SYMPTOMS TO DIAGNOSIS			AVERAGE TIME WASTE—DIAGNOSIS TO BEGINNING OF TREATMENT			TOTAL TIME WASTED
	DAYS	WEEKS	MONTHS	DAYS	WEEKS	MONTHS	MONTHS
Miller,* 1929	448	64.0	16.0	266	38.0	9.5	24.0
Collins,† 1934	250	35.6	8.9	103	14.7	3.8	12.7
Miller, 1940	196	28.0	7.1	112	16.0	4.0	11.1

*Reported (in 1933) from University of Iowa.
†From University of Iowa.

This represents a considerable improvement (see Table IV) when compared with a somewhat similar study made by me[1] in 1929 and by Collins[2] in 1934 at the University of Iowa. While the data in Table IV come from two widely separated clinics in two different states, it is fair to assume that the general trend toward earlier diagnosis and treatment is real.

Table V shows that *65 per cent of the patients are now undergoing treatment within three months* after seeking medical advice. Patients included in this series come

TABLE V.* TIME WASTE BETWEEN FIRST MEDICAL EXAMINATION AND INSTITUTION OF TREATMENT

One month	70 patients or 48.0%	65%
Two months	16 patients or 10.0%	
Three months	11 patients or 7.0%	
Four months	3 patients	
Five months	1 patient	
Six months	5 patients	
Seven months	5 patients	
Eight months	1 patient	
Nine months	3 patients	
Ten months	1 patient	
Eleven months	2 patients	
Twelve months	9 patients	
Delay of more than one year	20 patients	

*In calculating the percentages, all patients delaying more than one year before the institution of treatment were omitted in order to avoid excessive distortion.

largely from the lower economic rank, and this three-month delay is partly explainable on the basis of time required for filter board examinations and for making home, transportation, and hospitalization arrangements.

While the average age in this series was 54 years, the lesion often occurs in younger women. Among the 183 patients studied, 142, or 77 per cent, were fifty years of age or over. Forty-one, or 22 per cent, were forty-nine years of age or under. While this age division is arbitrary and does not necessarily draw the line between the pre- and the postmenopausal groups, it may be assumed that the majority fifty years or over were past the menopause, and similarly, many forty-nine years of age or under were still menstruating. This assumption is justified on the basis of the report by Crossen and Hobbs[3] on the relationship of late menstruation to carcinoma of the corpus.

Since so much importance has been attached to bleeding late in life, it was of interest to determine how many of these women had a curettage as part of their original diagnostic study. Curettage was done in only 40, or 28 per cent, of the women over fifty. In other words, 72 per cent with significant bleeding occurring after the fiftieth year of life did not have what is considered an important diagnostic procedure as a means of determining the cause of the symptom. Twenty-six, or 65 per cent, of the women forty-nine or under had no curettage as part of their original diagnostic study. While neglect is not necessarily indicated by failure to perform a curettage, it appears that the value of this procedure is not yet fully appreciated. Unquestionably many physicians felt that curettage was indicated but chose to refer the patient directly to a specialist for both diagnosis and treatment.

Fibroids Associated With Corpus Carcinoma.—Thirty-one, or 19.8 per cent, of 156 patients treated entirely by us had fibroids. Twelve, or 40 per cent, of these 31 patients are dead. Morton believes the outlook somewhat poorer in patients with fibroids, but we are not impressed with the fact that they particularly affect the prognosis.

Double Primary Carcinoma.—Five of our patients had more than one primary carcinoma. The combinations noted were breast 1, cecum 1, sarcoma in uterine fibroid 1, lymphoblastoma 1, and rectum 1. Three of these patients are dead, the two with rectal and cecal primaries are still living after appropriate treatment directed toward both uterine and intestinal lesions.

Metaplasia.—Definite metaplasia, sometimes marked with extensive areas of squamous epithelium in the uterine carcinoma, was noted in 15 per cent, or 23 times. The significance of this change is not entirely clear nor does it appear to affect the prognosis (16 living, 7 dead). Meigs[10] and Schattenberg and Ziskind[11] consider the prognosis somewhat poorer in adenoacanthoma, but we did not observe any such influence in our cases.

Histologic Classification of Tissues.—One hundred and fifty-six patients were treated entirely by us. The remaining 27 were treated in part elsewhere and were not included in the remainder of this analysis.

Tissues not originally classified were re-examined and graded by me. The basic criteria for grouping were generally similar to those commonly used.

TABLE VI. HISTOLOGIC GRADING IN 156 CASES OF CORPUS CARCINOMA TREATED BY US

	NO. CASES	PER CENT
Grade I	23	14.7
Grade II	78	50.0
Grade III	50	32.0
Grade IV	5	3.2
	156	99.9

Since a single section may reveal several grades of malignancy, it is natural that in grading there shall exist some difference of opinion. This emphasizes the desirability of broad grouping such as used by Scheffey and Thudium[4] (low, intermediate, high). Classification on this simplified basis is shown in Table VII.

TABLE VII

	MILLER		SCHEFFY AND THUDIUM	
	NO. CASES	PER CENT	NO. CASES	PER CENT
Low	101	64.7	22	32.3
Intermediate	50	32.0	27	39.7
High	5	3.2	18	26.4
		99.9		98.4

While our series reveals a high incidence of so-called lower grades and few highly malignant cases, I am satisfied that this is a matter of interpretation rather than due to any climatic or geographic factor which renders corpus carcinoma less malignant in Michigan.

The relationship between histologic grade and survival has been pointed out by others[7, 9] and is further born out by this study. Among the 68 eligible for five-year survival, the relationship between grade and survival is shown in Table VIII.

TABLE VIII. RELATION BETWEEN HISTOLOGIC GRADE AND SURVIVAL

HISTOLOGIC GRADE	NUMBER OF PATIENTS	PER CENT OF TOTAL	NUMBER SURVIVORS	PER CENT OF SURVIVORS FOR EACH GRADE	NUMBER DEAD
1	17	25	13	76	4
2	30	44	17	57	13
3	18	26	7	39	11
4	3	4	1	25	2
	68	99			

Clinical Classification.—Several clinical classifications have been attempted. Crossen's[5] clinical grouping is based on findings at the time of operation. Healy and Brown[6] base their classification on palpable size of the uterus and believe that a small or normal-sized uterus is associated with a better prognosis. All of our cases were carefully examined and, as an additional check on size, the length of the uterine cavity was measured. While this procedure was helpful, we do not necessarily advocate it as a routine procedure. On the basis of palpable size and length of uterine cavity, we were able to divide our patients into three groups, thus: Group I, normal size, revealing no palpable enlargement of the uterus and a uterine cavity measuring 3 inches or less; Group II, the moderately enlarged, including those with enlargement of the uterus up to size of a two and one-half months' pregnancy and a cavity measuring not more than 4½ inches; Group III, markedly enlarged, including all patients with a uterus larger than a three months' pregnancy, and a cavity measuring more than 5 inches.

TABLE IX. CLINICAL GROUPING ACCORDING TO UTERINE SIZE AMONG ALL 68 PATIENTS ELIGIBLE FOR PERCENTAGE FIVE-YEAR SURVIVAL (UNCORRECTED)

	NO. OF PATIENTS	PER CENT OF TOTAL	LIVING	PER CENT OF GROUP LIVING	DEAD
Group I (Normal). No palpable enlargement of uterus. Cavity measures 3 inches or less.	21	31	14	66	7
Group II (Moderately enlarged). Enlarged uterus up to 2½ mo. pregnancy. Cavity measures less than 4½ inches.	34	50	19	56	15
Group III (Markedly enlarged). Uterus size 3 mo. pregnancy or more. Cavity measures more than 5 inches.	13	19	3	23	10
	68	100	36		32

The findings presented in Table IX confirm the general opinion as well as that expressed by Healy and Brown[6] that corpus carcinoma found in a small or normal-sized uterus is generally associated with a better prognosis. That this is not always true, however, is proved by patients with moderate or even marked enlargement of the uterus who recover. Tables X, XI, XII, and XIII bear further on this aspect of the problem. It will be noted that these factors are generally significant only and are not infallible indicators of prognosis.

Extent of Lesion as Noted in Gross Specimen Removed at Operation.—Eighty-five of the 156 patients treated by us were operated upon and the specimens subjected to gross and microscopic study. The findings permitted classification into three groups as shown in Table X. However it must be noted that all but 10 of the 85 patients operated upon received preoperative irradiation, and consequently a much different grouping might have been noted had there been no such preoperative irradiation.

TABLE X. EXTENT OF LESION BASED ON MICROSCOPIC AND GROSS EXAMINATION OF SPECIMEN REMOVED AT TIME OF OPERATION (HYSTERECTOMY, BILATERAL SALPINGO-OOPHORECTOMY) IN 85 CASES

GROUP	NO. EACH GROUP	PER CENT
Group I. (No carcinoma found or local and/or superficial growth. No deep infiltration.)	40	47.0
Group II. (More extensive than I and less than III. Not more than halfway through uterine wall.)	19	22.3
Group III. (Widespread and/or deep infiltration through more than one-half uterine wall.)	26	30.0
	85	99.3

Thirty-nine of the 85 patients operated upon were eligible for five-year survival. Five were treated by operation only and the remaining 34 by some form of preoperative radiation followed by operation. Among these 39 cases, the extent of the gross lesion is revealed in Table XI.

TABLE XI. EXTENT OF NEOPLASTIC INVOLVEMENT IN THE 39 PATIENTS OPERATED UPON MORE THAN FIVE YEARS AGO AND THEREFORE ELIGIBLE FOR FIVE-YEAR SURVIVAL

GROUP	NO.	LIVING	PER CENT LIVING IN EACH GROUP	DEAD
Group I. (No carcinoma found or superficial, local.)	18	15	83.0	3
Group II. Moderately widespread. (Moderate invasion but not beyond one-half uterine wall.)	8	6	75.0	2
Group III. Widespread. Extensive. Deeply infiltrating. (More than one-half thickness of uterine wall.)	13	8	61.5	5

As expected, we noted a higher incidence of five-year survivors in Group I, but 61 per cent of Group III cases also survived five years or more. This is significant and should influence our attitude regarding therapy. Because the lesion is widespread and deeply invades the uterine wall does not necessarily mean a poor prognosis. In advanced cases, it would appear desirable that tumor cells be rendered inactive and operative manipulation be reduced to a minimum. By so doing the hazard of spill and manipulative spread should be decreased.

Correlation between uterine size and extent of the lesion was attempted in Tables XII and XIII. It will be noted that a large, easily palpated uterus does not always mean deep infiltration of the uterine wall. Likewise a normal-sized

uterus does not necessarily imply a superficial localized neoplasm, further evidence that such precautionary measures as preoperative radiation and minimal operative manipulation are desirable for successful therapy.

TABLE XII. CORRELATION BETWEEN SIZE OF UTERUS AND EXTENT OF LESION AMONG ALL 85 HYSTERECTOMIZED PATIENTS (CORRECTED FOR NONCARCINOMA DEATHS)

SIZE OF UTERUS	EXTENT OF LESION			TOTALS FOR SIZE OF UTERUS
	1	2	3	
1	1 dead 17 living or 94%	0 dead 4 living or 100%	2 dead 9 living or 81%	3 dead 30 living or 90%
2	1 dead 20 living or 95%	0 dead 10 living or 100%	3 dead 7 living or 70%	4 dead 37 living or 90%
3	0 dead 1 living or 100%	4 dead 1 living or 20%	1 dead 4 living or 80%	5 dead 6 living or 54%
Totals for extent of lesion	2 dead 38 living or 95%	4 dead 15 living or 78%	6 dead 20 living or 76%	

TREATMENT

Cure may be achieved by (a) removal or (b) destruction of the lesion in situ. For far-advanced cases and for those unable to withstand operation, irradiation is obviously the treatment of choice. The difficulty of adequately irradiating the uterine cavity is well known. The problem has not been solved by multiple applicators, multiple applications nor ingenious devices.

In very early lesions surgery alone may be satisfactory. For most patients, however, both irradiation and surgery are indicated. It is a mistake to look upon irradiation and surgical extirpation as competitive measures. Both have a place in treatment and both have proved their usefulness.[7] In general, best results should be achieved by using both surgery and irradiation, one supplementing the other.

During the period covered by this study, the usual forms of treatment were utilized. When possible, however, operation was preceded by irradiation (75 cases). We believe the evidence presented in this and other reports clearly indicates the desirability of utilizing both radiation and surgery, one supplementing the other. We prefer preoperative x-ray followed by total hysterectomy, six weeks after completion of the x-ray.

Preoperative irradiation reduces the hazard of dangerous spill and manipulative spread at the time of operation and also makes the operation easier by reducing congestion if carried out at the optimum time (six weeks following completion of irradiation). When reliance must be placed on irradiation alone, as in poor physical risks, x-radiation should be followed by an intracavitary radium application. The effect of radium upon endometrial carcinoma has been described by Arneson[8] as characterized by the breaking up of the glandular structure, swelling, pyknotic fragmentation of nuclei, necrosis, leucocytic infiltration, and slough. Similar changes may be noted following x-radiation. Indeed,

preoperative radiation may result in complete destruction of the neoplasm. This has been noted by many observers. We are impressed by such evidence of the effectiveness of radiation. Many patients who ultimately die from carcinoma following hysterectomy alone possibly do so because of unavoidable manipulative spread at the time of surgery. Because of its proved effectiveness, preoperative irradiation should reduce this hazard. Our observations have convinced us that surgical extirpation six weeks following completion of preoperative radiation is today the most desirable form of treatment for most corpus malignancies.

TABLE XIII. CORRELATION BETWEEN SIZE OF UTERUS AND EXTENT OF LESION AMONG 39 PATIENTS OPERATED UPON WHO WERE ELIGIBLE FOR FIVE-YEAR SURVIVAL (CORRECTED FOR NONCARCINOMA DEATHS)

SIZE OF UTERUS	EXTENT OF LESION			TOTALS FOR SIZE OF UTERUS
	1	2	3	
1	1 dead 7 living or 87%	0 dead 3 living or 100%	1 dead 3 living or 75%	2 dead 3 living or 86%
2	0 dead 9 living or 100%	0 dead 2 living or 100%	1 dead 5 living or 83%	1 dead 16 living or 93%
3	0 dead 1 living or 100%	3 dead 0 living or 0%	1 dead 2 living or 67%	4 dead 3 living or 42%
Totals for extent of lesion	1 dead 17 living or 94%	3 dead 5 living or 62%	3 dead 10 living or 76%	

While we are impressed with the effectiveness of radiation, we cannot overlook the fact that residual neoplastic tissue is often seen in the removed specimen. Preoperative irradiation may have destroyed much of the disease yet the frequency with which healthy-appearing carcinoma is found warrants the belief that irradiation alone, at least in its present mode of application, is not a thoroughly reliable remedy for corpus cancer. The absence of neoplasm in removed specimens following preoperative radiation may in some cases be more apparent than real. Unobserved localized cell nests may still be present which, if permitted to remain, will ultimately cause the patient's death. The fact that there exists a higher late death rate among the *operable* patients treated by irradiation only tends to emphasize this point.

Others have pointed out the correlation between histologic grade and survival rate. Our own observations have corroborated the serious outlook for patients with more highly undifferentiated types of carcinoma. Yet, we cannot subscribe to the view that histologic grade shall dictate choice of treatment. While tissue grading is helpful it is only one of several factors influencing prognosis. We are not impressed with the fact that early and intermediate grades of endometrial carcinoma are so much more radioresistant than the highly undifferentiated, a point which appears to have been emphasized by others. In our series, preoperative irradiation has destroyed all evidence of carcinoma as determined by study of the removed specimen in all histologic grades.

Much emphasis has been placed on the use of intracavitary radium, and we believe this desirable where dependence must be placed on irradiation alone or when the patient is too obese for adequate external x-radiation. When, however, surgical extirpation is planned, our preference is for preliminary x-radiation because of: (a) its detrimental effect upon the tumor cells, (b) its known effectiveness in reducing congestion, (c) ease of application, (d) absence of uterine manipulation, and (e) no necessity for anesthesia or operating room setup.

Results of treatment in this study are shown in Tables XIV and XV.

TABLE XIV. TYPE OF TREATMENT USED IN 156 CASES OF CORPUS CARCINOMA

TYPE OF TREATMENT		NO. TREATED
Radiation:		
Radium	22	
X-ray	9	
Radium and x-ray	40	71
Operation		10
Radiation + Operation		75
Total		156

TABLE XV. RESULTS OF TREATMENT AMONG 68 PATIENTS ELIGIBLE FOR FIVE-YEAR SURVIVAL

	NO. OF CASES	PER CENT OF TOTAL	LIVING	PER CENT OF GROUP LIVING	DEAD
Irradiation	29	42.6	10	34.4 (Corrected 37%)	19
Operation	5	7.3	4	80.0 (Corrected 100%)	1
Irradiation + Operation	34	50.0	24	70.5 (Corrected 82.3%)	10

Naturally patients too far advanced to be operated upon are included among those treated by irradiation. Yet, only seven of the 29 so treated by us fell into this classification. In the remaining 22, the reason was some physical factor preventing operation or else a flat refusal on the part of the patient (2 cases). By removing the 7 advanced cases, we find among the 22 patients treated by irradiation only 7 living and 15 dead or a five-year survival rate of 32.4 per cent as compared with 70.5 per cent (corrected 82.3 per cent) for combined irradiation and operation. Two, or 6.8 per cent, of the irradiated group have since died of carcinoma, whereas no such late carcinoma deaths have occurred among the operated or combined irradiated and operated groups. The five patients treated by operation only reveal 4 five-year survivors, too small a number to permit comment.

One patient hopelessly advanced was not treated. If this case be included in our group eligible for five-year survival, we find an absolute survival rate (five years) from all methods of treatment of 52.1 per cent.

Regardless of uterine size, histologic grade, or gross extent of the lesion we are able to report:

1. There were 34.4 per cent five-year survivals following irradiation treatment alone. Corrected for noncarcinoma deaths, this figure becomes 37 per cent. However, two in this group have since died of carcinoma.

2. There were 70.5 per cent five-year survivals following combined irradiation and operation. Corrected, this figure becomes 82.3 per cent. None of these five-year survivors have yet died of carcinoma.

Response of Grade IV Carcinoma to Treatment.—Only four of our 156 patients were considered to have true Grade IV carcinoma. One of these patients is living and well today seven years following treatment by preoperative x-ray and operation. The response to x-ray in this case appears to have been remarkable since the uterus revealed no carcinoma when studied following hysterectomy. Two patients were treated by x-ray, radium, and operation. One died within a year and the other, four years after treatment. The fourth patient refused operation and received x-ray only. She lived one year following treatment.

MORTALITY

We have definite information regarding 45 deaths in our series. Carcinoma was the chief cause in 71 per cent. Other causes are revealed in Table XVI.

TABLE XVI. CAUSE OF DEATH IN 45 PATIENTS WITH CARCINOMA OF THE UTERINE BODY

CAUSE	NUMBER IN GROUP TREATED BY IRRADIATION ONLY	NUMBER IN GROUP TREATED BY IRRADIATION + OPERATION	TOTAL	PER CENT
Carcinoma	23	9	32	71.1
Heart	3	3	6	13.3
Pneumonia	1	1	2	4.4
Embolism	1	1	2	4.4
Intestinal Obstruction	0	2	2	4.4
Carcinoma of Stomach	1	0	1	2.2
			45	99.8

OPERATIVE MORTALITY

There were three operative deaths among the 85 hysterectomized patients (10 hysterectomy only, 75 irradiation plus hysterectomy), an operative mortality of 3.5 per cent.

Cardiac failure, ninth postoperative day	1 case
Pneumonia, tenth postoperative day	1 case
Peritonitis and intestinal obstruction, fifth postoperative day	1 case
Total	3

All three deaths occurred in patients who had received no preliminary irradiation as part of their treatment. There was no immediate mortality following irradiation.

MORBIDITY

Morbidity in carcinoma patients is not easy to evaluate. In our series morbidity was high and much of it attributable to radiation. The proponents of surgery alone may here find a potent argument against combining the two forms of treatment. Because of the difficulty in determining primary cause, no attempt is made to discuss morbidity at this time. For distribution see Table XVII.

TABLE XVII. MORBIDITY NOTED IN 156 PATIENTS WITH CARCINOMA OF THE UTERINE BODY

I. Gastrointestinal:	
	Severe diarrhea
	Intestinal obstruction
	Rectal stricture
	Fistula
	Anorexia
II. Genitourinary:	
	Urethrocystitis, etc.
	Stricture (ureteral)
	Hydronephrosis
	Fistula
	Abscess (paranephritis)
	Incontinence
III. Skin:	
	Wound infection
	Severe dermatitis
	Toxic erythema
	Erysipelas
IV. Nervous system:	
	Pain, severe, necessitating:
	Strong sedation, morphine
	Alcohol injections
	Chordotomy
V. Bones:	
	Metastasis
	Fractured femur
VI. Respiratory:	
	Pneumonia
	Pulmonary embolism
	Lung metastases

SUMMARY AND CONCLUSIONS

1. The basis for this study was 183 cases of corpus carcinoma, of which 156 were treated entirely by us and 68 were eligible for five-year survival.

2. The average time waste from onset of symptoms to beginning of treatment was approximately eleven months. This is an improvement when compared with previous reports on time waste.

3. Sixty-five per cent of patients in this series had commenced treatment before the fourth month after onset of symptoms.

4. (a) Histologic grading of endometrial carcinoma is only one of several factors helpful in determining prognosis. (b) We are not impressed with the fact that histologic Grades I and II are particularly radioresistant.

5. Clinical grouping based on size of the uterus is practical. Our findings tend to bear out the general feeling that corpus carcinoma in a small or normal-sized uterus is associated with a somewhat better prognosis.

6. Methods of treatment and results are discussed and the following views expressed: (a) For inoperable cases of corpus carcinoma whether due to complicating illness or extent of disease, x-ray followed by intracavitary radium is the procedure of choice. By this method we obtained 34.4 per cent five-year survivors (37.0 per cent when corrected for noncarcinoma deaths). (b) For operable cases with possible exception of extremely early lesions, we advise preoperative irradiation followed by total hysterectomy six weeks after completion of the radiation treatment. (c) X-ray is preferred to intracavitary radium for preoperative irradiation whenever possible. (d) By combining preoperative irradiation with surgery, we are able to report 70.5 per cent five-year survivors (82.3 per cent when corrected for noncarcinoma deaths). (e) Radiation and surgery should not be looked upon as competitive forms of therapy but as remedial measures of proved value. Best results are obtained by using both in a supplementary manner.

7. Fibroids were found in 19.8 per cent of our cases. We cannot say that fibroids affect the prognosis.

8. Five patients had a double primary.

9. Metaplasia was common, occurring in 15 per cent. Its significance was not clear. It did not appear to affect prognosis.

10. Study of mortality revealed carcinoma as the cause of death in 71.1 per cent of 45 patients with complete data. Other causes included heart disease, pneumonia, embolism, intestinal obstruction, etc.

11. Primary operative mortality in 85 patients was 3.5 per cent (1 cardiac, 1 pneumonia, 1 peritonitis).

REFERENCES

(1) *Miller, Norman F.:* J. Iowa M. Soc. **23:** 132, 1933. (2) *Collins, R. M.:* Ibid. **24:** 71, 1934. (3) *Crossen, Robt. J., and Hobbs, John E.:* J. Missouri M. A. **32:** 361, 1935. (4) *Scheffey, Lewis C., and Thudium, Wm. J.:* Am. J. Obst. & Gynec. **34:** 1006, 1937. (5) *Crossen, H. S.:* Ibid. **33:** 587, 1937. (6) *Healy, Wm. P., and Brown, Robert L.:* Ibid. **38:** 1, 1939. (7) *Healy, Wm. P., and Cutler, Max:* Ibid. **19:** 457, 1930. (8) *Arneson, A. N.:* Am. J. Roentgenol. **36:** 461, 1936. (9) *Morton, Daniel G.:* Am. J. Roentgenol. **41:** 789, 1939. (10) *Meigs, J. V.:* Tumors of the Female Pelvic Organs, New York, 1934, The Macmillan Co., p. 140. (11) *Schattenberg, Herbert J., and Ziskind, Joseph:* Am. J. Obst. & Gynec. **39:** 112, 1940.

DISCUSSION

DR. WILLIAM P. HEALY, New York, N. Y.—If I understand Dr. Miller correctly he states that he much prefers preoperative roentgen irradiation to intrauterine radium irradiation. He is not discussing the treatment of cancer of the corpus uteri by roentgen ray alone, but merely the preparation of the surgical field for the hysterectomy which is to follow within six weeks. It must be thoroughly understood that he does not recommend roentgen therapy for the cure of cancer of the corpus uteri. For this purpose one must combine the roentgen therapy with intrauterine therapy.

I must disagree with one of the reasons which Dr. Miller gives for not using intrauterine preoperative irradiation with radium. He states that he avoids anesthesia and manipulation of the uterus. Yet after all we must make a diagnostic curettage and for this the patient usually is under an anesthetic.

In these patients who have passed the menopause one should have radium available and ready to be placed in the uterus while awaiting the pathologist's report. I am very much against depending upon preliminary roentgen irradiation alone in these cases, even though one is planning a hysterectomy.

Histologic grading, as Dr. Miller says, is one of several factors in determining prognosis. It is a helpful factor and may be of importance in this way. If a patient has been curetted elsewhere and a diagnosis returned of adenocarcinoma of Grade I or II, we are justified in going forward with a hysterectomy immediately, without any preliminary roentgen or radium irradiation. That is the procedure which I follow. I think that hysterectomy in the operable cases will cure 90 per cent or more of those cases.

A uterus with a cancer of the corpus which does not exceed a two and one-half months' gestation in size is a very favorable case for cure by any method of procedure, provided it is a competent method such as a complete hysterectomy, either with or without irradiation, depending upon the histology of the case. In Group II I have placed all uteri larger than two and one-half months' gestation, and in Group III those patients with metastases.

I hope that you will all consider the clinical grading as well as the histologic grading of your cases in trying to make your prognoses. If you will do that there is no doubt that the end results will be improved; especially in cases where the uterus is not more than a two and one-half months' gestation in size. The hysterectomy should not be done too soon after irradiation. We usually wait about eight weeks.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—The analysis of Dr. Miller's material corresponds in general with our own experience on the Gynecologic Service at Jefferson Medical College Hospital. We, too, have no untraced patients. Four per cent of our patients were under 41 years; 24 per cent were under 50; 72 per cent were over 50. Only one of our group was a negress. Our nulliparous incidence is a bit higher than Dr. Miller's—27 per cent.

I am glad that Dr. Miller's present study shows an improvement in respect to the time wasted before treatment was instituted. A report made by us three years ago showed a situation very similar to his earlier findings, with the added interesting feature that the waste of time in patients with postmenopausal bleeding was nearly twice as great as that in patients with atypical premenopausal bleeding.

The frequent failure to perform or advise diagnostic curettage when urgently indicated has been proved by Dr. Miller's figures, and our records likewise emphasize this appalling neglect. At this point I wish to call attention to two factors which may either delay diagnosis or be responsible for the initiation of incorrect therapy. I refer, first of all, to ill-advised hormonal therapy, administered in the belief that the atypical bleeding is functional, and second, to the assumption that the presence of a myoma is the sole cause of atypical or postmenopausal bleeding. Myomas were associated with fundal carcinoma in 25 per cent of our series, a somewhat higher incidence than that reported by Dr. Miller.

At Jefferson we are in accord with Dr. Miller's premise that preoperative radiation is both desirable and essential. Generally we prefer preoperative radium to preoperative x-ray, but Dr. Miller has made out a good case for x-ray. We agree entirely that whenever the extent of the lesion and the condition of the patient permit, surgical extirpation should follow in six to eight weeks. The plan of treatment followed at Jefferson is as follows:

1. Diagnostic dilatation and curettage with radium available.
2. Rapid histologic report.
3. Preliminary radiation with radium.
4. Subsequent panhysterectomy or further radiation dependent upon individualization.

Dr. Miller's figures show the decided advantage in his hands of combined irradiation and operation, regardless of clinical or histologic classification. With the higher grade malignancies, we feel that preoperative radiation offers more than

surgery alone. With regard to the low grade lesions, radiation, in our experience, has been equally as effective as surgery alone, or as effective as combined radiation and surgery.

Our results are not as good as Dr. Miller's. As a matter of interest I have tabulated the results according to the grade of malignancy and to the type of treatment, not with the idea of drawing conclusions but merely to show trends. These tables are appended (Tables I, II and III).

TABLE I. RESULTS OF TREATMENT OF FUNDAL CARCINOMA

62 Patients seen, 1 untreated, 100% follow-up

Five-year salvage (Including cancer deaths)	25 patients	40.9% / 40.3%
Five-year salvage (Excluding cancer deaths)	21 patients	33.8% / 34.4%
Five-year salvage (Now alive, 5 to 15 years)	15 patients	24.1% / 24.5%

TABLE II. FIVE-YEAR SALVAGE IN RELATION TO TYPE OF TREATMENT

TYPE OF TREATMENT	NUMBER OF PATIENTS	INCLUDING CANCER DEATHS	EXCLUDING CANCER DEATHS	PRESENT-DAY SALVAGE
Radiation and surgery	18	8 (44.4%)	6 (33.3%)	5 (27.7%)
Radiation	30	14 (46.6%)	12 (40.0%)	7 (23.3%)
Surgery	13	–	–	3 (23.0%)

TABLE III. FIVE-YEAR SALVAGE IN RELATION TO GRADE OF MALIGNANCY

GRADE OF MALIGNANCY	NUMBER OF PATIENTS	INCLUDING CANCER DEATHS	EXCLUDING CANCER DEATHS	PRESENT-DAY SALVAGE
Low	19	13 (57.8%)	11 (61.3%)	9 (47.3%)
Intermediate	24	6 (25.0%)	4 (16.6%)	2 (8.3%)
High	17	–	5 (29.4%)	3 (17.6%)

(One patient unclassified, alive 15 years)

DR. KARL H. MARTZLOFF, PORTLAND, OREGON.—I would like to ask Dr. Miller whether the anatomic specimens which he obtained following preoperative x-ray radiation showed the same degree of cancer destruction as after intrauterine radium irradiation? It seems to me that if the destruction of the cancer is the primary object, then intrauterine radium irradiation is the method of choice. If the rationale of deep x-ray therapy is primarily for its effect upon the uterine circulation, then of course I can see his intention there. Certainly Dr. Miller's excellent salvage statistics bear out the correctness of his procedure.

DR. MILLER (closing).—In reply to the question raised by Dr. Martzloff, it may be said that the neoplasm is decidedly affected by preoperative radiation regardless of type. Probably the intracavitary radium gives a greater local reaction than the externally applied x-ray. The latter, however, is evenly distributed whereas the intracavitary radium may be very active in one area and leave another portion unaffected.

PRIMARY CANCER OF THE FALLOPIAN TUBE*

A Consideration of Its Incidence, Clinical Diagnosis, and Treatment, With the Report of a Case Diagnosed Before Operation

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FROM a purely clinical aspect, primary cancer of the Fallopian tube offers three points of major interest; namely, its apparent infrequency, the difficulty of its clinical diagnosis, and the unsatisfactory status of its treatment.

One cannot but be impressed by the observation that, while the Fallopian tube, together with the fundus and the cervix uteri, is a segment of the Müllerian duct system and its epithelium, like theirs, is of coelomic origin, the cervix uteri is the portion of the female generative tract most frequently involved, the Fallopian tube the portion least frequently involved in malignant disease.

This is well shown by Haupt[1] who found 3 instances (0.22 per cent) of primary tubal cancer among 1,361 cases of all types of genital cancer in von Franqué's clinic. On the other hand, Schmidt[2] reported 10 instances (1 per cent) of primary tubal cancer among 995 genital cancers operated upon at the University Frauenklinik in Berlin.

The first case of primary tubal cancer to be described adequately was reported in 1886 by Orthmann.[3]† While many attempts have been made to assemble the case reports that have accumulated in the literature since then, the results obtained vary considerably. An accurate appraisal of the total number of primary tubal cancers is not easy to make when one realizes, as has been stressed by Doran[4] and others, that the same case may be reported separately by more than one author, that reported cases may be overlooked, and that cases of questionable acceptability may be included. To illustrate the foregoing, a few of the numerous excellent compilations that have appeared from time to time are cited; namely, those of Doran,[4] Fromme and Heynemann,[5] Dietrich,[6] Wechsler,[7] Liang,[8] Vest,[9, 10] Wharton and Krock,[11] Nürnberger,[12] Harms,[13] Robinson,[14] and Schmidt.[2] All of these reveal the same unavoidable discrepancies. It should be noted, however, that Nürnberger in his critical study was able to compile 301 cases up to and including the first part of 1931. As far as we can ascertain, by the end of 1935 the total number of reported cases varied from 331 to 349. From 1935 to 1938 inclusive, we were able to collect from the *Cumulative Index Medicus* reports of 32 new cases by the following authors: 1 case each by Wlassow,[15] Stolz and Machátová,[16] Beitzke,[17] Dannreuther,[18] Held,[19] Powers and Harrison,[20]

*Read at the Sixty-Fifth Annual Meeting of the American Gynecologic Society held at The Seigniory Club, Quebec, Canada, June 17 to 19, 1940.

†This reference gives a microscopic study. Many authors, however, refer to a later publication by Orthmann under the impression that the reference here cited gives inadequate data.

Janota and Reček,[21] Sarikadioglu,[22] Phaneuf,[23] Jeanneney and Soubiran,[24] Müller,[25] Altkaufer and Szejnberg;[26] 2 cases each by Robinson,[14] Harms,[13] Charache,[27] Bazterrica and others;[28] 3 cases by Lenczowski;[29] and 9 cases by Schmidt.[2] These reports were all verified by consulting the original sources.*

INCIDENCE

Once attention is focused on a given process its apparent earlier rarity appears to diminish in the face of its more frequent recognition. Schroeder[31] was of the opinion that primary cancer of the Fallopian tube never occurred. According to various estimates in the literature, the incidence ranges from 1.33 per cent (Zangemeister[32]) to 0.34 per cent (Martin[33]) of operations on diseased tubes. We have been unable to verify the figures attributed to Martin.

It is generally overlooked that the often quoted figures of Zangemeister are derived from a twelve-year compilation of operative material from the University Frauenklinik, Leipzig. In this study 5 instances of cancer of the tube were found among 374 operations for various types of tubal disease. While this gives an incidence of 1.33 per cent, it is well to remember that the material represents an annual average of about 31 operations. That this is probably a fortuitous circumstance is suggested by the experience of Danckwardt[34] who found one primary tubal cancer among 5,000 gynecologic laparotomies performed in the same clinic from 1926 to 1932. For the thirty-four-year period prior to 1926, according to Zweifel,[35] only 7 instances of this disease had been seen in the same clinic. Frankl[36] stated that he had seen 12 instances over a period of twenty years, while Askanazy[37] had observed only two examples in his laboratory over a period of thirty-five years. Bazterrica and others[28] reported 2 instances (0.45 per cent) among 437 cases of tubal affection. Eleven cases were encountered in the Gynecologic Clinic of the Johns Hopkins Hospital during the fifty years of the hospital's existence. Five of these had occurred prior to 1929.[11] From January, 1930, to January, 1940, according to TeLinde,[38] 6 more cases were found among 14,365 gynecologic operative specimens. It appears probable, therefore, if one allows for unreported as well as unrecognized cases, that the upper limit of primary tubal cancer incidence may be in the neighborhood of 0.5 per cent.

CLINICAL DIAGNOSIS

It has been stated repeatedly that the diagnosis of primary cancer of the Fallopian tube has never been made before operation. Undoubtedly exceptions have occurred.† On the other hand, Fonyó[40] stated that up to the time of his study cancer of the Fallopian tube was diagnosed in only 6.5 per cent of the reported instances. Without attempting to reconcile these two opposing points of view, we wish to point out that in a certain small group of patients a tentative clinical diagnosis of primary cancer of the Fallopian tube can be made with a fair degree of accuracy. This is illustrated by the case herein reported.

Various authors have attributed diagnostic import to age; the patient's state of nutrition; intermittent, localized, cramplike pain followed

*The publication by Leuret,[30] while indexed, is not included here since no case report is presented. The case of Sarikadioğlu[22] is so briefly reported that its acceptability may be questioned.

†Hoffman[39] stated that a definite diagnosis was made in one of the cases reported by Anspach and himself. Dannreuther[18] also stated that in his case the suspicion of primary tubal malignancy was confirmed by operation.

and relieved by vaginal discharge; and site, shape, and rapid development of the tumor. Others have emphasized sacral pain, back pain, and pain radiating along the sciatic or femoral nerves, obviously symptoms too unspecific to be of help.

An analysis which we made of 233 of the 301 cases tabulated by Nürnberger and of 31 of the 32 cases reported from 1935 to 1938 indicates that clinically these patients with primary cancer of the Fallopian tube can be divided into two groups: (1) those who have no abnormal vaginal discharge, and (2) those who have an abnormal vaginal discharge. In the first group, irrespective of whatever other symptoms and signs are present, there is little to warrant clinical differentiation from other types of adnexal disease.

The second group comprises somewhat more than half of the analyzed cases. In about one-fifth of these, the discharge was described merely as "leucorrhea," obviously not a symptom to arouse suspicion in view of its frequency and varied manifestations.

In about two-fifths of these cases, the discharge was described as bloody, and had occurred as a metrorrhagia during the menstrual life of the patient or after the menopause. Diagnostic curettage, judging from our analysis of these cases, ordinarily gives no clue to the underlying pathology,* and in the absence of abnormal manual pelvic findings may lull one into a sense of false security. In fact, abnormal uterine bleeding, though associated with physical findings that signify abnormality of the intra-abdominal generative tract, obviously is not sufficiently suggestive to warrant suspecting cancer of the tube. The same may be said of pelvic pain. Intermittent, cramplike discomfort, however, when not related to menstruation or to some of the atypical forms of postovulatory, intermenstrual discomfort, may be a helpful diagnostic symptom when it is followed and relieved by a blood-tinged, watery discharge, as occurred in one of the patients of Anspach and Hoffman.[43]

In another one-fifth of the cases, there was a history of either a profuse serous or watery vaginal secretion, a symptom in itself difficult to evaluate prior to the establishment of an anatomic diagnosis. It is a symptom which Doran and others have noted, and, of course, one which raises the old argument of the possible existence of a benign hydrops tubae profluens. Hydrops tubae profluens probably does occur in those patients with cancer of the tube who have a profuse serous or serohemorrhagic vaginal discharge.

The remaining one-fifth of the cases, in our opinion, were those offering diagnostic promise. In these, bloody discoloration of the watery (serous) secretion was recorded. This represented not only secretion from the tubal epithelium, but also, probably, the products of autolytic change secondary to tumor necrosis, capillary damage, transudation, and hemorrhage. Obviously, few symptom-sign complexes are diagnostic of a malignant visceral neoplasia. However, if one can exclude recent gestation and organic disease of the vagina and uterine cavity, especially

*In a rare instance in which extension of the cancer to the endometrium has occurred, as reported by Smith,[41] Kittler,[42] Lenczowski,[29] or Wharton and Krock,[11] diagnostic curettage might reveal a cancer. Ordinarily this would be, and has been, confused with primary endometrial malignancy.

incipient ulcerating cancer complicated by cervical stenosis, then a copious, serosanguineous uterine discharge becomes suspiciously pathognostic. For it can then be ascribed to an extrauterine origin, logically tubal, and a malignant complication may be inferred, as was done in our case.

Hysterosalpingography as an aid in diagnosis is not mentioned in the literature, and was not used by us. It should be of inestimable value, however, when no physical signs other than a vaginal discharge are detectable.

If, therefore, the possibility of an extrauterine lesion is kept in mind, and if, too, hysterosalpingography is utilized, the generally justifiable pessimism concerning the practicability of making a clinical diagnosis of primary cancer of the Fallopian tube should not extend to those patients presenting the syndrome of hemohydrops tubae profluens.

THERAPY

The question arises as to what constitutes adequate treatment. It is accepted that total hysterectomy and adnexectomy are logical procedures when feasible. The question also arises as to the advisability of using high voltage roentgen therapy after operation. This was not used on our patient, despite its recommendation by numerous writers, because of the absence of factual support for such a recommendation. After careful search of the literature, we are unable to find satisfactory evidence of its value. There are several reasons for the lack of satisfactory information concerning the value of deep roentgen ray therapy. Among these are: (1) The number of patients so treated, because of the infrequency of the disease, is, according to Burnam,[11] too small to warrant conclusions; (2) writers who report the cases of patients operated upon several years previously often do not report the status of their patients at the time of the report; and (3) the period between the treatment given a patient and the reporting of her case is in numerous instances too brief to allow an estimate of the ultimate outcome.

Table I illustrates the present status of this problem. It is seen here that 22 patients had received postoperative radiation treatment. Of these, 10 (45 per cent) were known to be dead, and 8 (36 per cent) were alive at the time of the report. In 7 instances (31 per cent), the outcome of the treatment was not stated. Of the 8 living patients, 5 had been alive less than one year, while 3 had been alive eight, three, and two years at the time of the reports. In brief, the information available here is too inadequate to warrant any conclusions as to the value of radiation therapy. Obviously an eight-year survival, as in Schmidt's Case 4, is not conclusive. The same may be said of Kaplan's[44] patient who lived somewhat over four years. Radiation treatment had been given to this patient five months after operation. While these cases are cited as encouragement for the combined use of surgery and radiation, the danger of drawing conclusions from such isolated experiences is clear when one compares them with the experience of Powers and Harrison.[20, 45] Their patient lived over four years before manifesting a local recurrence which did not respond to radiation therapy. Furthermore, there are reports of patients who lived for long periods after operation without subsequent radiation therapy. Six of the patients in Nürnberger's[12] study lived five or more years without postoperative radiation treatment, while 14 lived three years. Jahkola[46] reported the case of one patient who was alive and well seven years (one patient who had had radiation therapy was living after six years). Haupt's[31] patient lived twenty years, Norris'[47]

TABLE I. CASES REPORTED SINCE 1935 WHERE AUTHORS USED OR ADVISED USE OF POSTOPERATIVE RADIATION THERAPY

AUTHOR'S NAME AND YEAR OF REPORT	NUMBER OF CASES	TYPE OF OPERATION	TYPE OF RADIATION THERAPY	TIME BETWEEN TREATMENT AND CASE REPORT	DURATION OF LIFE AFTER TREATMENT	LIVING AT TIME OF REPORT	NOW DEAD	REMARKS
Held (1935)	1	Salpingo-oophorectomy right	Radium, 7,200 mc.	1+ yr.	1+ yr.	0	+	No influence on disease by radiation.
Beitzke (1935)	1	Hysteromyomectomy salpingo-oophorectomy	Roentgen	9 mo.	?	?	?	
Powers and Harrison (1935)	1	Supravaginal hysterectomy, salpingo-oophorectomy	Roentgen for recurrence 3 yr. after operation	1 yr.	4+ yr.	+	+	Radiation did not influence recurrent process. Died of generalized carcinomatosis[3]
Charache (1936)	2	(1) Left salpingectomy, appendectomy. One wk. later panhysterectomy, removal of remaining adnexa	Roentgen, 1,720 units	1 yr.	3 yr.	+	+	Died of abdominal recurrence.[1]
		(2) Supravaginal hysterectomy. Salpingo-oophorectomy	None	5 yr.	2 yr. & 8 mo.	0	+	Died following operation for intestinal obstruction, not due to malignancy
Schmidt (1936)	9	(1) Panhysterectomy. Salpingo-oophorectomy	Roentgen 2 series		3 yr.	0	+	[4]
		(2) Panhysterectomy. Salpingo-oophorectomy	None		1¼ yr.	0	+	

[1]Personal communication from Dr. Herman Charache.
[2]Personal communication from Dr. Louis E. Phaneuf.
[3]Personal communication from Dr. John H. Powers.
[4]Previously reported by Hornung, 1927.

		(3) Panhysterectomy. Salpingo-oophorectomy	Roentgen 2 series	?	3 mo.	0	+	
		(4) Right salpingo-oophorectomy	Roentgen 2 series	8 yr.	8 yr.	+	0	
		(5) Panhysterectomy. Salpingo-oophorectomy	Roentgen 2 series	7 yr.	3-4 yr.	?	?	
		(6) Hysterectomy. Right salpingo-oophorectomy	Roentgen 2 series	7 yr.	7 wk.	0	+	
		(7) Panhysterectomy. Salpingo-oophorectomy	Radium for recurrence	4 yr.	?	0	+	Peritoneal implants present at time of operation.
		(8) Panhysterectomy. Salpingo-oophorectomy	Roentgen	3 yr.	3 yr.	+		
		(9) Panhysterectomy. Salpingo-oophorectomy	Roentgen 3 series	2 yr.	2 yr.	+		
		(10) Panhysterectomy. Salpingo-oophorectomy Nov., 1935	Radium Sept., 1935 for cancer of cervix. Roentgen after operation	Less than 1 yr.	Less than 1 yr.	+		Prognosis poor, signs of recurrence present at time of report.
Janota and Reček (1936)	1	Panhysterectomy. Salpingo-oophorectomy	Roentgen	¾ yr.	¾ yr.	+	0	
Harms (1937)	2	(1) Panhysterectomy. Salpingo-oophorectomy	Roentgen castration 6 mo. preoperatively		?	?	?	Both patients had diagnostic curettage for bleeding. Roentgen ray for presumed benign metrorrhagia.
		(2) Panhysterectomy. Salpingo-oophorectomy	Roentgen castration preoperatively		?	?	?	

TABLE I—CONT'D

AUTHOR'S NAME AND YEAR OF REPORT	NUMBER OF CASES	TYPE OF OPERATION	TYPE OF RADIATION THERAPY	TIME BETWEEN TREATMENT AND CASE REPORT	DURATION OF LIFE AFTER TREATMENT	LIVING AT TIME OF REPORT	NOW DEAD	REMARKS
Altkaufer and Szenjnberg (1937)	1	Panhysterectomy. Salpingo-oophorectomy	Roentgen	Less than 1 yr.		+		
Müller (1937)	1	Panhysterectomy. Salpingo-oophorectomy	Roentgen	Less than 1 yr.		+		
Lenczowski (1938)	3	(1) Panhysterectomy. Salpingo-oophorectomy	Roentgen intensive		?	0	+	
		(2) Panhysterectomy. Salpingo-oophorectomy	Roentgen intensive		?	0	+	
		(3) Panhysterectomy. Salpingo-oophorectomy.	Roentgen intensive	Less than 1 yr.	Less than 1 yr.	+		
Bazterrica et al. (1938)	1	Panhysterectomy. Salpingo-oophorectomy	Roentgen	7 yr.	Not stated	?	?	No statement concerning patient's status
Jeanneney and Soubiran (1938)	1	Supravaginal hysterectomy. Left Salpingo-oophorectomy	Recommend radiation but say nothing of its use on this patient	Less than 1 yr.	?	?	?	No statement concerning patient's status.
Phaneuf (1938)	1	Panhysterectomy. Salpingo-oophorectomy	Roentgen 6,200 R.U.	1+ yr.	9 mo.		+	Extensive involvement. Died of metastatic carcinomatosis.[2]

lived nineteen years, Dannreuther's[48] lived six years, and Wharton's[49] lived thirteen years without radiation therapy. Wharton and Krock[11] reported the case of a patient who had died after five years, but not of cancer. They also reported the cases of 2 patients who had been alive and well four and three years, respectively, at the time of their study.

CASE REPORT

History.—Mrs. M. D., white, aged 54 years, was first seen on May 2, 1931 because of a bloody vaginal discharge. Her family history was irrelevant. In 1915 she had had a left salpingo-oophorectomy, in 1920 an appendectomy, and in 1924 a cholecystectomy. She had never been pregnant, and had ceased menstruating in 1924, at the age of 47. No further vaginal bleeding had occurred until one year prior to consultation (six years after the menopause) when she had begun to have a scanty, intermittent, odorless, bloody, vaginal discharge.

Physical Examination.—The vagina contained a slightly blood-stained secretion. The uterus was felt to be small, symmetrical, and in second degree retroposition. The parametrial regions presented no notable change, and the right ovary could not be outlined. The remainder of the examination and routine urine and blood examinations, including a Wassermann test, were of no significance.

Impression.—The clinical impression was postmenopausal metrostaxis of undetermined origin.

Diagnostic curettage on May 6, 1931, produced no grossly identifiable endometrial tissue. Microscopic examination of the cervical tissue which had been excised showed no noteworthy pathology. Pelvic examination under anesthesia at this time was not noteworthy. The uterine canal measured between 3.5 and 4 cm. in length. There was no evidence of cervical stricture.

Subsequent Course.—Each speculum examination following the curettage revealed some blood in the vagina, of which the patient was not cognizant. About a month after the curettage the patient again noted a bloody vaginal discharge. She continued to bleed regularly though intermittently, having an occasional day with no bleeding. Speculum examination two and a half months later revealed a brownish, watery discharge coming from the cervical canal. The passage of a sound into the cervical canal and the bimanual examination were not noteworthy. A note was made at this time that while this postmenopausal bleeding might be caused by an uncomplicated, local, endometrial, vascular process, in view of the watery character of the discharge, the possibility of tubal malignancy should not be overlooked and the possibility of a nonpalpable ovarian neoplasm (granulosa cell tumor) should be considered. The patient felt well and was gaining weight. She was examined once more in March, 1932; then was not seen again until July 1, 1935.

The history at this time was unchanged except that during the four months before July, 1935, she had felt she was losing urine from the bladder in small involuntary gushes. Examination revealed a blood-tinged watery secretion. A uterine sound met obstruction at about the level of the internal os which was passed with some difficulty. The uterine cavity now measured approximately 6 cm. in length. There was no evidence of pent-up secretion. Upon bimanual examination a tender, smooth, adherent, somewhat elastic mass, measuring about 4 to 6 cm., was noted in the right cul-de-sac. Cystoscopic examination was irrelevant. Five cubic centimeters of methylene blue were left in the bladder without evidence of methylene blue leakage per vaginam. The impression was again recorded that this was probably a cancer of the right Fallopian tube, and operation was advised. An ovarian cyst, however, could not be excluded. The increased length of the uterine cavity, together with the difficulty of passing a uterine sound, suggested a partial cervical stenosis.

On Dec. 10, 1935 the patient gave the same history and stated that she felt well. The findings were also the same. Operation was again advised.

The patient returned on Aug. 5, 1936, stating that she had been severely jarred in an automobile accident seven weeks previously. One week after the accident the blood-tinged watery discharge had ceased, and since then there had been considerable abdominal discomfort of a constant, dull, aching character. Examination was essentially the same as before, except that the right pelvic mass now bulged into the right lateral vaginal fornix, and there was induration in the right posterior

fornix. The mass was adherent but not fixed. It was felt that the process now was one of borderline operability, probably inoperable. A provisional diagnosis of cancer of the Fallopian tube was made, and operation was again advised.

Operation.—Six days later (Aug. 11, 1936) a supravaginal hysterectomy and right salpingectomy were performed. The essential finding at operation, aside from numerous parietovisceral and viscerovisceral adhesions which made the operation difficult, was the densely adherent right tube. In situ the tube measured about 8 cm. in diameter in its ampullar portion. It resembled an ordinary hydrosalpinx, and so overlay the small uterus as to completely obscure it. For purposes of exposure, it was expedient to remove the tube separately, the tubal section being performed between hemostats in the grossly normal isthmic portion. A supravaginal hysterectomy was done in preference to a total removal, despite the suspicion of tubal malignancy, because this procedure was simpler and safer in the presence of the existing anatomic distortion and adhesions. The tube as removed was grossly intact. No left tube or ovary was demonstrable, while a right ovary could not be identified. No palpable retroperitoneal glands were felt, and there was no gross evidence of peritoneal carcinomatosis. Convalescence was uneventful, and the patient was discharged from the hospital on the eleventh postoperative day. She was last seen in March, 1940, at which time she felt well and was gaining weight. Abdominal and pelvic examinations were irrelevant.*

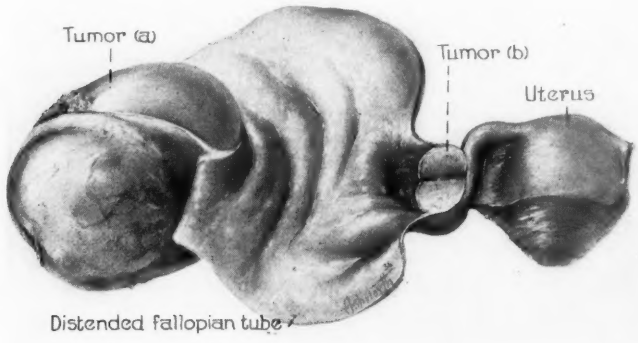

Fig. 1.—Illustrating primary carcinoma of right Fallopian tube. Primary tumor at *a*. Distended Fallopian tube has been opened longitudinally and is seen to retract from Tumor *a* where the latter is unattached and projects into the lumen of the tube. Secondary tumor at *b* occluding lumen of tube.

Pathologic Study.—Gross Examination: The fresh, gross, tubal specimen, examined immediately after the completion of the operation, resembled an ordinary hydrosalpinx with a closed fimbriated end. Except for numerous fibrous tags, its surface was smooth. Over the point represented as Tumor *b* in Fig. 1, the tube decreased rather suddenly in caliber. Beyond this point the isthmic portion of the tube was of about normal caliber. Incision of the distended portion of the tube released a copious amount of watery, blood-stained fluid, while the infundibular portion revealed a soft, yellowish gray, friable material.

The shrunken, formalin-fixed specimen measured 9.5 cm. in length and from 1.5 to 4.5 cm. in diameter in its enlarged portion. At what corresponded to the infundibular portion of the tube was a tumor mass (*a*, Fig. 1) measuring 5.5 by 3.5 by 4 cm. The mass was softly elastic and smooth, and its serosa presented no evidence of neoplastic involvement. On section, the wall of the tube retracted immediately from the tumor proper. The cut surface of the tumor was yellowish

*Since preparation of this paper the patient has developed a left-sided cervical lymphadenopathy. Tissue removed for biopsy revealed an obvious metastatic carcinoma resembling the section shown in Fig. 6. Pelvic, abdominal, and laryngoscopic examinations and roentgenographic examination of the chest are at present irrelevant. Satisfactory temporary response has occurred to roentgen ray therapy.

gray and opaque. There was a central area of hemorrhage and a narrow peripheral zone which was gray, glistening, and translucent. Over this zone the tumor was adherent to the tubal wall.

The previously distended portion of the tube had shrunken considerably. It had a slightly corrugated, pale gray, and glistening mucosa, and measured 6 cm. in circumference and 1 to 1.5 mm. in thickness. At the extreme uterine end of this dilatation, there was a smaller tumefaction (*b*, Fig. 1) which measured 1.5 by 1.5 by 1.8 cm. It appeared to be well circumscribed, confined within the lumen of the tube, and on section presented a pale gray, glistening, translucent surface.

The uterus was small, measuring 3.5 by 2.8 by 2 cm. In the fixed specimen the uterine cavity measured 2 cm. in length, and the myometrium 0.8 cm. in thickness. The endometrium was smooth and could be seen distinctly. In its thickest portion it measured about 1.5 mm.

Histologic Examination: Sections through the tube wall and Tumor *a* (Fig. 1) showed Fallopian tube muscularis along one side; occasional moderately dense aggregations of mononuclear white blood cells, some of the plasma cell type, in the inner half of the tube wall; and only a scanty lymphocytic infiltration in the outer half of the wall. The serosa was not definitely identifiable.

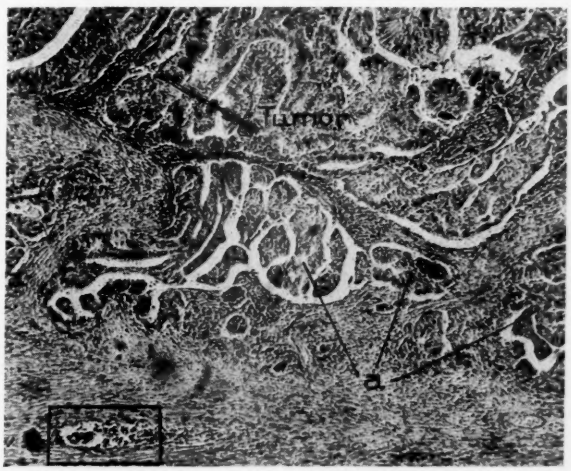

Fig. 2.—Section from Tumor *a*, Fig. 1, and wall of attached Fallopian tube. Blocked area is a blood vascular space containing tumor cells. *a* indicates tumor process invading wall of tube (×60).

The luminal aspect of the sections showed an obvious neoplasm with a papillary arrangement (Figs. 2 and 4). The papillae were composed of central connective tissue cores with capillaries, dense round (plasma) cell infiltration, and a peripheral epithelial covering of large round and fat spindle-shaped cells several layers in thickness. These cells were irregular in size, shape, staining reaction, and polarity. The chromatin distribution was coarse and often scanty. Nucleoli occurred but were not constant, while mitotic figures were abundant. Toward the center this cellular area ceased abruptly to pass over progessively into a zone of inflammatory change and then a zone of necrosis. Only the inner half of the tubal wall showed invasion. A few psammoma bodies were noted in the areas of round cell infiltration of the tumor interstitium and also in the more central area of necrosis.

Sections from the thin-walled, fluid-containing portion of the tube showed a slightly undulating inner surface (Fig. 5) lined by a single layer of flat or low columnar cells. Only a rare club-shaped fold was seen. A moderate subepithelial round cell infiltration also involved the remainder of the tube wall.

Sections from the smaller Tumor *b* showed a cytology similar to that in the larger Tumor *a*. However, its papillary character was not so obvious as in Tumor

a for here the cells occurred in broad strands and compact alveoli (Fig. 6). There was no necrosis, and the musculature of the tube showed discrete, dense aggregations of lymphocytes.

Sections from the isthmic portion of the tube proximal to Tumor *b* showed no evidence of anatomic abnormality.

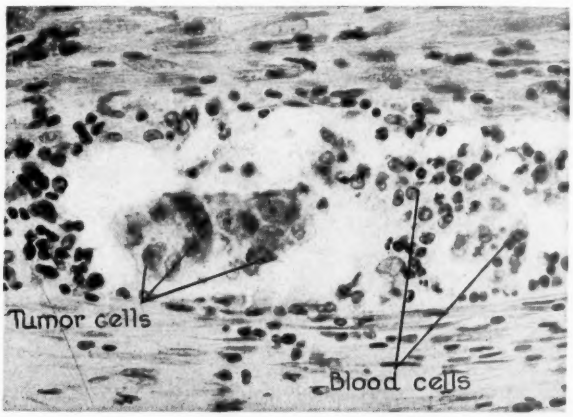

Fig. 3.—High power of blocked area in Fig. 2 (×480).

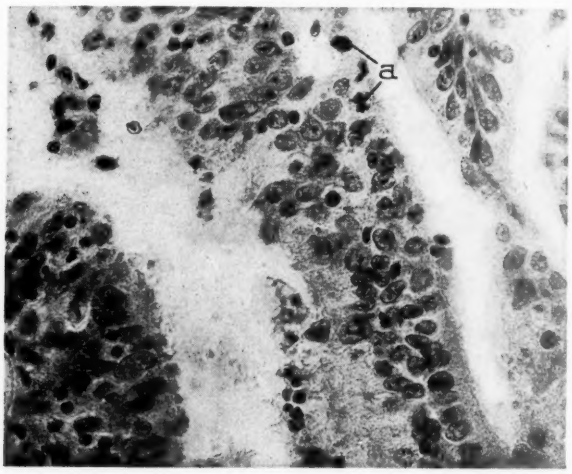

Fig. 4.—High power of tumor in Fig. 2 showing multilayered tumor cells. Mitoses at *a* (×480).

Sections from the uterus revealed the endometrium to vary from the minor fraction of a millimeter to over a millimeter in thickness. The glands varied from narrow straight tubules to moderately tortuous structures with moderately widened lumina. All were lined with columnar epithelium. In addition, there were numerous large, dilated glands which in general were lined by a single layer of epithelium varying from low columnar to flat. No mitotic figures were seen. The interglandular stroma had the appearance of fibrous connective tissue, and in its superficial portion showed the picture of bona fide endometritis.

Pathologic Diagnosis.—Primary carcinoma (papillary) of the right Fallopian tube associated with a secondary, intralumenary-occluding tumor nodule and hydrosalpinx; salpingitis, chronic, probably secondary to neoplastic change; senile atrophy of the uterus; endometritis, chronic; glandular hyperplasia of the endometrium (?).

Clinical Pathologic Summary.—The neoplasm represents a primary carcinoma of the Fallopian tube occurring in a woman past the menopause, whose symptoms were of six years' duration, who was under observation for five years, and whose condition was tentatively diagnosed a year before operation. The diagnosis was based on the history and the observation of a watery, blood-stained cervical discharge unexplained by diagnostic curettage and physical examination.

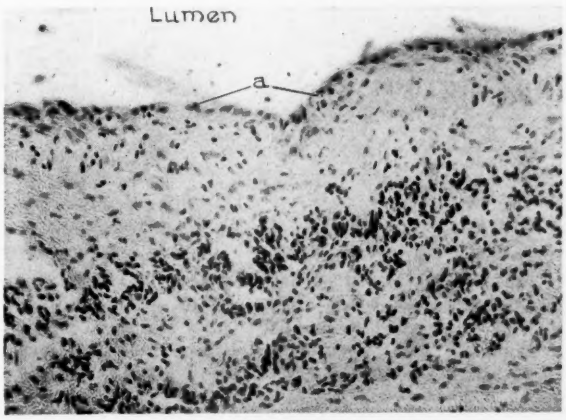

Fig. 5.—Section through wall of distended Fallopian tube, showing at *a* single layered flattened and cuboidal epithelium. Aggregations of leucocytes further out in tube wall (×235).

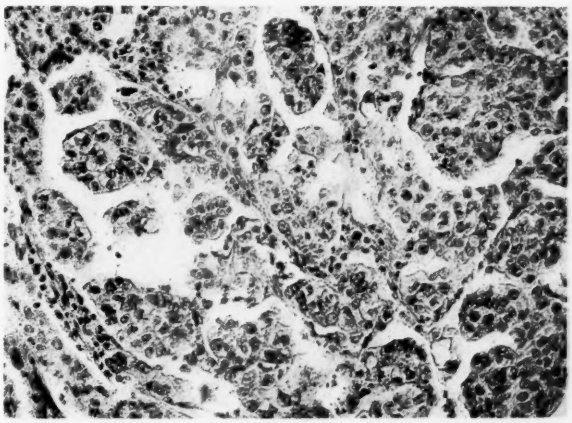

Fig. 6.—Section through Tumor *b*, Fig. 1 (×235).

It is impossible to say whether this patient's initial bleeding originated from an incipient tubal neoplasm or whether it represented a coincidental endometrial hemorrhage, as occurs in some forms of benign postmenopausal bleeding. However, in view of the uninterrupted character of the bleeding, and its gradual evolution to a predominately serous discharge, it is probable that it originated in the tube. The peripheral necrosis of the parent Tumor *a* explains the source of the serous, blood-stained secretion and the secondary phenomenon of hydrops tubae profluens which became increasingly profuse apparently as the size of the tumor and its degenerative changes progressed. The sudden cessation of the discharge one week after an injury is explained by the development of the secondary Tumor *b* which occluded the tubal lumen. Whether Tumor *b* represents a free tumor transplant, a metastatic process, or a separate malignant focus cannot be definitely determined.

It also cannot be definitely stated whether the endometritis was secondary to contact with the products of tumor degeneration passing from the tube into the uterine cavity or secondary to a possible cervical stenosis.

SUMMARY AND CONCLUSIONS

A case is reported of primary carcinoma of the Fallopian tube which was tentatively diagnosed before operation. The patient is alive and well four years after operation (see footnote, p. 812).

The symptoms and signs of this comparatively rare disease, as one obtains them from the literature, are so protean, and in general so similar to other types of adnexal disease that there is little logical basis for suspecting its existence.

A tentative diagnosis of primary carcinoma of the Fallopian tube, however, can logically be considered in that limited group of patients who present the syndrome of hydrops tubae profluens with a serosanguineous vaginal discharge but no causative vaginal or uterine pathology.

Hysterosalpingography should have a definite place in the establishment of a provisional clinical diagnosis, especially if palpable pelvic abnormality is not demonstrable.

The high degree of malignancy of this disease, as generally stated in the literature, is in some instances probably more apparent than real when one considers, as in the case herein reported, the long duration of the disease before operation.

The use of high voltage roentgen ray therapy is recommended by numerous authors. However, there is at the present time no suitable information available that indicates its value in the treatment of this disease.

REFERENCES

(1) *Haupt, W.:* Zentralbl. f. Gynäk. **57:** 742, 1933. (2) *Schmidt, Kurt:* Ztschr. f. Geburtsh. u. Gynäk. **112:** 339, 1936. (3) *Orthmann:* Centralbl. f. Gynäk. **10:** 815, 1886. (4) *Doran, A.:* J. Obst. & Gynaec. Brit. Emp. **17:** 1, 1910. (5) *Fromme, F., and Heynemann, T.:* Veit's Handb. d. Gynäk. **5:** 182, 1910. (6) *Dietrich, H. A.:* Die Neubildungen der Eileiter, Biologie und Pathologie des Weibes, Berlin, 1926, Halban-Seitz **5:** Part 1, p. 13. (7) *Wechsler, H. F.:* Arch. Path. **2:** 161, 1926. (8) *Liang, Z.:* Virch. Arch. f. path. Anat. **259:** 577, 1926. (9) *Vest, C. W.:* Johns Hopkins Hosp. Bull. **25:** 305, 1914. (10) *Vest, C. W.:* Malignant Growths on the Fallopian Tube, in Lewis' Loose Leaf Surgery, Hagerstown, Md., 1927, W. F. Prior Co., Inc. **2:** Chapt. 1, p. 1. (11) *Wharton, L. H., and Krock, F. H.:* Arch. Surg. **19:** 848, 1929. (12) *Nürnberger, L.:* Veit-Stoeckel Handbuch der Gynäkologie, ed. 3, **7:** 679, 1932. (13) *Harms, C.:* Zentralbl. f. Gynäk. **61:** 2628, 1937. (14) *Robinson, M. R.:* Am. J. Obst. & Gynec. **32:** 84, 1936. (15) *Wlassow, W.:* Monatschr. f. Geburtsh. u. Gynäk. **98:** 217, 1934. (16) *Stolz, J., and Machátová, O.:* Bratisl. lekár. listy. **15:** 465, 1935. (17) *Beitzke, H.:* Schweiz. med. Wchnschr. **65:** 513, 1935. (18) *Dannreuther, W. T.:* Am. J. Obst. & Gynec. **30:** 724, 1935; personal communication, 1939. (19) *Held, E.:* Gynéc. et obst. **32:** 395, 1935. (20) *Powers, J. H., and Harrison, F. F.:* Clin. Misc. Mary I. Bassett Hosp. **2:** 30, 1935. (21) *Janota and Reček:* Casop. lék. česk. **75:** 1205, 1936. (22) *Sarikadioğlu, Halis Tevfik.:* Türk tib cem. mec. **3:** 156, 1937. (23) *Phaneuf, Louis E.:* Am. J. Surg. **39:** 620, 1938. (24) *Jeanneney and Soubiran:* J. de méd. de Bordeaux **115:** 5, 1938. (25) *Müller:* Spisy lék. fak. Masaryk. Univ. **16:** 57, 1937. (26) *Altkaufer, H., and Szejnberg, H.:* Ginek. polska **16:** 924, 1937. (27) *Charache, H.:* Ann. Surg. **103:** 290, 1936. (28) *Bazterrica, E., Barcas, E., and Ferracani, R. S.:* Rev. méd.-quir de pat. fem. **12:** 439, 1938. (29) *Lenczowski,*

J.: Ginek. polska **17:** 517, 1938. (30) *Leuret, J.:* Gaz. méd. de France **44:** 285, 1937. (31) *Schroeder, C.:* Handbuch der Krankheiten der Weiblichen Geschlectsorgane, ed. 2, Leipzig, 1875, p. 324. (32) *Zangemeister, W.:* Beitr. z. klin. Chir. **34:** 96, 1902. (33) *Martin, A. E.:* Pathologie u. Therapie der Frauenkrankheiten, ed. 4, Berlin, 1907, p. 387. (34) *Danckwardt, L.:* Monatschr. f. Geburtsh. u. Gynäk. **95:** 84, 1933. (35) *Zweifel, E.:* Cited by Danckwardt, Ref. 34. (36) *Frankl, O.:* Henke-Lubarsch Handb. d. Spez. Path. Anat. u. Hist. **7:** 847, 1930. (37) *Askanazy:* Cited by Liang, Ref. 8. (38) *TeLinde, R. W.:* Personal communication, 1940. (39) *Hoffman, J.:* Discussion, AM. J. OBST. & GYNEC. **26:** 360, 1933. (40) *Fonyó, J.:* Zentralbl. f. Gynäk. **37:** 1317, 1913. (41) *Smith, W. S.:* AM. J. OBST. & GYNEC. **24:** 267, 1932. (42) *Kittler, E.:* Zentralbl. f. Gynäk. **51:** 971, 1927. (43) *Anspach, B. M., and Hoffman, J.:* AM. J. OBST. & GYNEC. **22:** 424, 1931. (44) *Kaplan, I. I.:* In discussion, Ref. 41. (45) *Powers, J. H.:* Personal communication, 1939. (46) *Jahkola, A.:* Acta Soc. med. fenn duodecim **16:** 1, 1931. (47) *Norris, C. C.:* Discussion, AM. J. OBST. & GYNEC. **26:** 358, 1933. (48) *Dannreuther, W. T.:* Personal communication, 1939. (49) *Wharton, L. R.:* Personal communication 1939 concerning case reported in 1929, Ref. 11.

808 MEDICAL DENTAL BUILDING

DISCUSSION

DR. ISIDOR C. RUBIN, NEW YORK, N. Y.—During the years 1928 to 1939 inclusive, 8,356 patients were admitted to the Gynecologic Service of Mt. Sinai Hospital. There were 410 cases of carcinoma of the female genital tract. One case of primary carcinoma of the Fallopian tube was encountered and 4 secondary cases.

In order to note the relative incidence of tubal carcinoma, it was compared with the incidence of carcinoma of the ovaries, uterus, cervix, and external genitalia (Table I).

TABLE I

	PRIMARY CASES	SECONDARY CASES
Carcinoma of ovary	125	12
Carcinoma of corpus uteri	88	4
Carcinoma of Fallopian tube	1	4
Carcinoma of cervix		151
Carcinoma of vagina		10
Carcinoma of vulva		14
Carcinoma of clitoris		1

Among the private patients, there were during 1928-1939, 333 cases of genital carcinoma. In 5 of this group the tubes were secondarily involved. In 2 cases because of metastatic involvement, the pathologist reported that the lesion was probably primary; and in only one case was an unequivocal diagnosis made of primary carcinoma of the Fallopian tube.

The case of primary tubal carcinoma on the Ward Service was referred by me to the hospital Jan. 11, 1933, with the diagnosis of a left-sided ovarian carcinoma. She was a 61-year-old unmarried woman, eight years after her menopause. She complained of lower abdominal pains for six months previous to her admission. The pains were located more often in the left than the right lower abdominal quadrant and were intermittent and cramplike in character. There were pelvic heaviness, frequent urination and constipation for two years and occasional slight bleeding from the rectum. There was no vaginal discharge.

At operation a left ovarian cyst the size of a grapefruit was found, adherent to the uterus, partly intraligamentous. The sigmoid and omentum were adherent to the cyst and about a quart of free amber colored peritoneal fluid was present. The left tube was found thickened and lay upon the anterior surface of the left ovarian cyst to which it was densely adherent. Its distal end was torn in the manipulation and appeared to contain soft, partially necrotic and perhaps carcinomatous tissue. Seven centimeters from the fundus it bulged to the size of a

walnut and appeared to be hemorrhagic. The involvement became less marked from this point toward the torn fimbriated end.

The uterus and both adnexa were removed. The pathologic report was primary adenocarcinoma of the left tube with implantation and lymphatic metastases to the uterus, right tube, and the large left ovarian cyst.

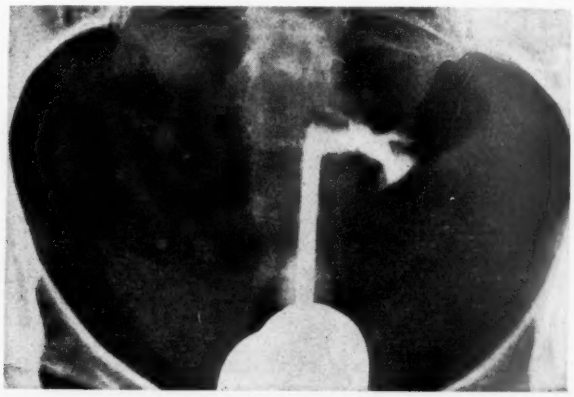

Fig. 1.—Hysterogram with 2 c.c. of contrast medium. Note the irregular ragged outline of the uterine cavity.

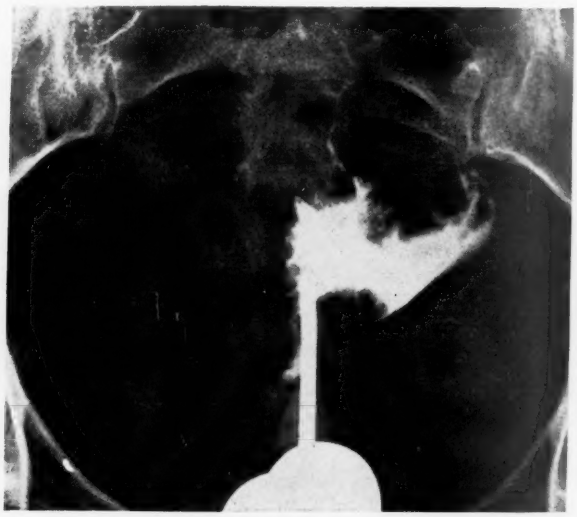

Fig. 2.—Hysterogram with 6 c.c. of contrast medium.

The follow-up notes show that despite postoperative x-ray therapy there were progressive weakness, weight loss, abdominal distention, epigastric distress, and five months after the operation general abdominal carcinosis. The patient was admitted to Dr. King's Hospital, Bay Shore, Oct. 16, 1933, where she died a month later. An autopsy was not made.

Bleeding in primary carcinoma of the tube without secondary involvement of the uterus presupposes patency of the tubal lumen. The lesion of the tube need not be necessarily large to cause bleeding, in which respect it resembles Paget's disease of the nipple where the papillary lesion is minute.

The outstanding symptom which differentiates papillary ovarian carcinoma from papillary carcinoma of the tube appears to be intermittent bleeding. I have rarely

encountered a case of papillary ovarian carcinoma which gave rise to uterine bleeding. In the differential diagnosis one must exclude on the one hand granulosa cell tumors, and on the other hand the rare combination of uterine papillary carcinoma with metastatic ovarian papillary carcinoma and vice versa. Both conditions were stressed by Dr. Martzloff. In contrast to papillary adenocarcinoma, the granulosa tumor is rarely adherent. Hormonal assay may help to distinguish estrogenic bleeding from that due to carcinoma.

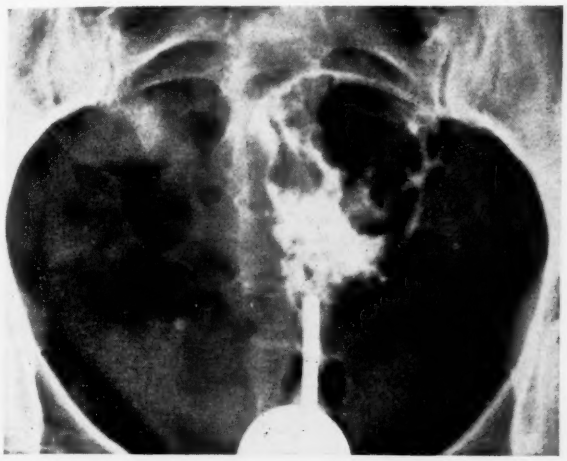

Fig. 3.—Hysterogasogram after 10 c.c. of contrast medium and 30 c.c. of CO_2. Note the defects in the configuration of the uterine cavity and the well-marked coating of the surface mucosa.

Fig. 4.—The carcinomatous uterus opened up; compare with Fig. 3.

A word as to uterotubal radiography in relation to malignancy which Dr. Martzloff thinks may be of value in differentiating uterine from tubal carcinoma. Since the availability of soluble crystalloid iodine compounds, I have again taken up injection of intrauterine radiopaque media as a diagnostic aid.

I wish to refer in this connection to a case in which carcinoma of the corpus was suspected. The patient was 49 years old, and began to bleed after three years of menopause. She bled for three months before her admission to the hospital. Her uterus was enlarged to the size of a six weeks' gestation while the adnexa were

negative. A hysterogram was made with fractional filling of 2, 4, 6, and 10 c.c. contrast fluid. The differential contrast with 30 c.c. of carbon dioxide was strikingly suggestive.

Without going into the technical consideration and the question of possible dislocation of carcinoma, I believe that we may safely use hippuran or other analogous substances for this purpose.

Reflecting upon the rare occurrence of primary tubal carcinoma, despite the relatively great frequency of salpingitis, one wonders whether chronic inflammation has any etiologic importance. On the other hand, the question why the Fallopian tube enjoys this apparent immunity while other derivatives of the Müllerian tract are frequently attacked by carcinoma, must remain unanswered for the present.

DR. WILLIAM A. SCOTT, TORONTO, CANADA.—Dr. Martzloff's compilation was made at the end of 1938, and in February, 1939, Dr. D. Nelson Henderson reported 2 cases from our service, both of which had occurred within a period of fourteen months. Dr. Henderson has recently had another case in his private practice, as yet unreported.

The diagnosis always presents great difficulties. The most common symptom is vaginal bleeding, usually occurring in patients past the menopause. The patients in each of our reported cases were 57 years of age. The preoperative diagnosis on our second case was granulosa cell tumor of the ovary, made on the basis of postmenopausal bleeding, negative findings on curettage, and palpation of a small tumor, thought to be ovarian. When no tumor is palpable, the diagnosis is usually carcinoma of the fundus of the uterus, and diagnostic curettage may not always differentiate between these two conditions, as secondary involvement of the endometrium may occur. If no tumor is palpable, and diagnostic curettage is negative, the patient may be treated expectantly or by radiotherapy and valuable time may be lost.

The frequency with which tubal carcinoma is associated with evidences of previous inflammatory disease is apparent from the study of the literature. In both of our cases the gross appearance of the tubes suggested previous inflammatory disease, and one patient gave a history of a post-partum pelvic inflammation.

It is obvious that the prognosis is bad in all these cases, and the value of radiotherapy after operation has yet to be established. In our first case the diagnosis was not made even with the abdomen opened, and consequently a supravaginal hysterectomy with removal of tubes and ovaries was carried out. Twenty-two months later there was recurrence in the cervix, which was treated with radium and deep x-ray therapy, and the patient then remained well for two years before developing widespread secondaries. The second case was diagnosed at the time of operation, and a total hysterectomy done. She remained well for three years and then developed multiple secondaries.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—In the last year I have seen two cases of primary carcinoma of the tubes, both private patients. In one there were no symptoms whatever except abdominal pain and the finding of a palpable mass to one side of the uterus. The other patient had the typical history described, except that her intermittent discharge was not blood stained but watery in character. This patient had had three attacks of what appeared to have been pelvic inflammatory disease. She ran a fever over several weeks, then it subsided, and I saw her for the first time after this episode. Feeling a mass at the side of the uterus I made a diagnosis of inflammation. She remained comfortable without fever until two months later when she had another febrile attack. We observed her through the second attack of fever until the temperature subsided but the watery discharge continued. Surgery was decided upon. The preoperative diagnosis was pelvic inflammatory disease with possible hydrosalpinx, but we found a primary carcinoma of the tube.

There was no question about the primary site of the disease in either case. In the second the tube when removed looked like the ordinary pus tube but on opening it we were surprised to find it filled with a soft mass of carcinoma.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—There have been two specimens of primary carcinoma of the tube in my laboratory in the last five years. One, a private patient of mine, is alive and free from any recurrence four years after supravaginal hysterectomy and bilateral salpingo-oophorectomy.

I would like to ask Dr. Martzloff whether or not he feels that the exact diagnosis of adnexal tumor, suspected of tubal malignancy, is of sufficient importance to justify the use of any mechanical means in diagnosis, either lipiodol or gas? I have a feeling that there may be a very definite possibility of spreading cancer cells into the peritoneal cavity from such a procedure.

DR. MARTZLOFF (closing).—Dr. Sears' question of whether an exact diagnosis is sufficiently important to warrant hysterosalpingography, of course, raises a point that must occur to everyone. I would consider the procedure justified on the basis of what is commonly found at these operations. Dr. Watson stated that his clinical diagnosis was that of pelvic inflammatory disease, which is a situation frequently encountered. In our case the diseased tube at operation resembled a huge hydrosalpinx. In view of the fact that cancer of the Fallopian tube is so commonly associated with a perisalpingitis and occlusion of the abdominal ostium, hysterosalpingography carefully done is probably relatively safe and therefore desired in a patient who has this watery discharge and in whom nothing can be felt on examination. The need for early diagnosis probably outweighs the possible theoretical hazard of forcing cancer into the peritoneal cavity by this type of examination.

FIBROMYOMA ANGIOMATOSUM OF THE UTERUS*

GEORGE H. GARDNER, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the Northwestern University Medical School and the Gynecologic Service of Passavant Memorial Hospital)

THIS is an interpretation of the unusual microscopic picture encountered in three submucous uterine tumors. Grossly, these tumors appeared to be partially degenerated fibroids. Microscopically they are composed of a smooth muscle and fibrous tissue stroma; however, there are few bundles of muscle fibers in transverse, longitudinal, and oblique sections, as is usual in a fibromyoma. Innumerable normally developed arteries are disseminated throughout these tumors and constitute their most striking microscopic characteristic; many of the arteries are quite large, others are small.

Such tumors are difficult to classify; they appear to be potentially malignant.

MATERIAL

TUMOR 1.—(I am indebted to Drs. H. O. Jones and John I. Brewer for the clinical data about this patient.) A 40-year-old nullipara was first admitted to St. Luke's Hospital in November, 1931, because of the usual systemic symptoms from a profound secondary anemia. A "fibroid polyp," the size of a small orange, presented in the external os and was removed by clamping and cutting its narrow pedicle.

She was readmitted in May of 1936, four and one-half years later, because of weakness and palpitation, again the result of marked secondary anemia. Fibromyomas were palpated in a uterus the size of a two and one-half months' pregnancy. Transfusions were given and a subtotal hysterectomy was performed. A soft polypoid tumor was found in the fundic portion of the uterine cavity; at its base there was invasion of the uterine muscle. This infiltrating tumor was sarcoma.

Her third admission occurred in November, 1937. The pelvis and lower abdomen were filled by firm tumor nodules; ascites was present; metastases were palpated in the vagina. She died in March, 1938, approximately six and one-half years after the vaginal myomectomy. The cause of death was generalized sarcomatosis, proved at autopsy.

Grossly, the original tumor, removed in 1931, was firm and spherical; red gray edematous tissue and streaks of yellow were noted on its cut surfaces. Microscopically, there is not much tissue which one can interpret as usual for a fibromyoma. The tumor appeared to be lobulated (see Fig. 1); each lobule was demarcated by a zone of necrotic tissue and consisted of an artery surrounded by a collar of pale-staining fusiform cells with elongated nuclei (see Fig. 2); these cells were arranged more or less radially in relation to the vessel. In the periarterial collars of essentially uniform-sized, pale-staining cells, one encounters an occasional mitotic figure.

There were several fibromyomas in the uterus removed in 1936, but the striking lesion was a soft gray polypoid tumor in the uterine cavity; it was attached to the fundus over a broad area. This tumefaction measured 6 by 4.5 by 4.5 cm. and, beneath it, tumor tissue invaded the uterine musculature. There was striking similarity, microscopically, between this necrotic polypoid tissue in the fundus of the uterus (see Fig. 3) and the original polypoid growth of 1931 (see Figs. 1 and 2). The tumor invading the myometrium was a typical spindle-cell sarcoma, with an abundance of mitoses.

*Presented, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Province of Quebec, Canada, June 17 to 19, 1940.

The vaginal metastasis of 1937 was also a spindle-cell sarcoma (see Fig. 4).

TUMOR 2.—A 36-year-old para i, gravida i, not pregnant for thirteen years, was admitted to Passavant Memorial Hospital on Dec. 6, 1937, as a private patient of Dr. Arthur H. Curtis. (I wish to thank Dr. Curtis for permission to include these data.) She complained of profuse menstruation, and intermenstrual bleeding. A polypoid uterine tumor presented in the external os; it was excised.

Grossly this tumor was described as the size and shape of a cervical stump; it was solid and edematous. Microscopically there was almost a complete absence (see Fig. 5) of the usual whorl pattern of a uterine fibromyoma. The large number of thick-walled arteries was striking; between the vessels there were smooth

Fig. 1.—(Tumor 1.) This tumor appears to be lobulated (×36). (Photographed by Clarence B. Mitchell.)

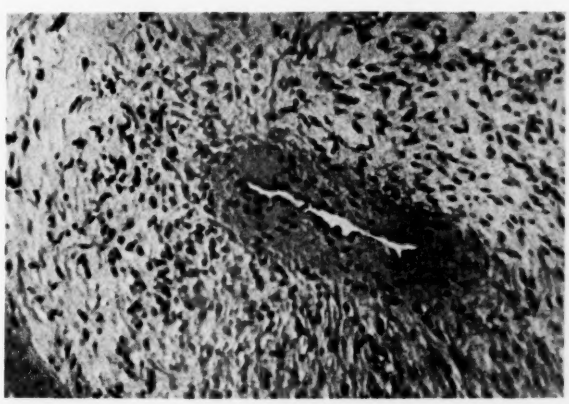

Fig. 2.—(Tumor 1.) A periarterial collar of pale-staining fusiform cells with elongated nuclei (×108). (Photographed by Clarence B. Mitchell.)

muscle fibers and fibrous tissue cells of fairly uniform size. In places the stroma was compact, elsewhere it was loose (see Fig. 6). There were a few zones of focal necrosis; in other areas the tumor was edematous. If one searches diligently he will find an occasional mitotic figure, but they are very rare.

In view of the peculiar microscopic appearance of this polypoid tumor and the clinical course of Tumor 1, Dr. Curtis advised his patient to return for a vaginal hysterectomy; this was performed on Jan. 6, 1938. Gross and microscopic study of the uterus failed to reveal anything abnormal. This patient is reported to be well.

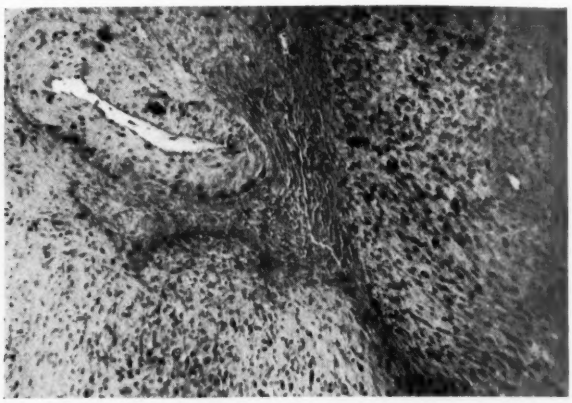

Fig. 3.—Necrotic polypoid tumor in the uterine cavity (×70). Note the striking similarity to the "polypoid fibroid" (see Fig. 1) removed four and one-half years previously. (Photographed by Clarence B. Mitchell.)

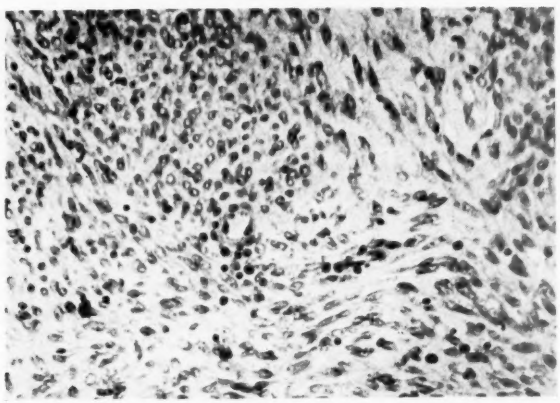

Fig. 4.—Vaginal metastasis of spindle-cell sarcoma (×172). (Photographed by Clarence B. Mitchell.)

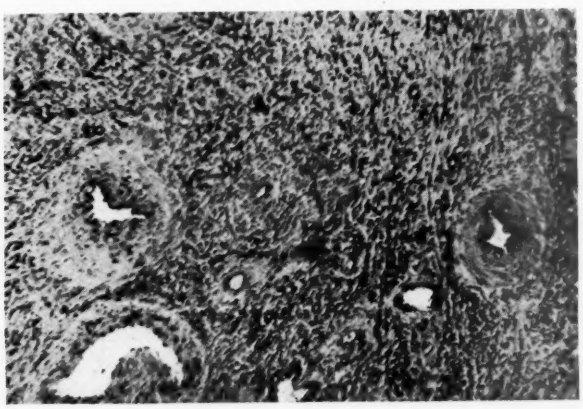

Fig. 5.—(Tumor 2.) The arrangement of stromal cells is not typical for a uterine fibromyoma. The large number of normally developed arteries is striking (×52). (Photographed by Clarence B. Mitchell.)

TUMOR 3.—A 41-year-old nullipara was admitted to the Gynecologic Service at Passavant on Jan. 8, 1959; her complaints included lower abdominal pain and irregular, profuse menses. The uterus contained fibromyomas and extended three fingerbreadths above the symphysis. A subtotal hysterectomy was performed. Fig. 7 is a drawing of the opened gross specimen. Attention is directed to the 1½ inch tumor in the posterior wall of the uterus; it was chiefly intramural but bulged into the uterine cavity (see *A* on Fig. 7) at the level of the internal os. Grossly

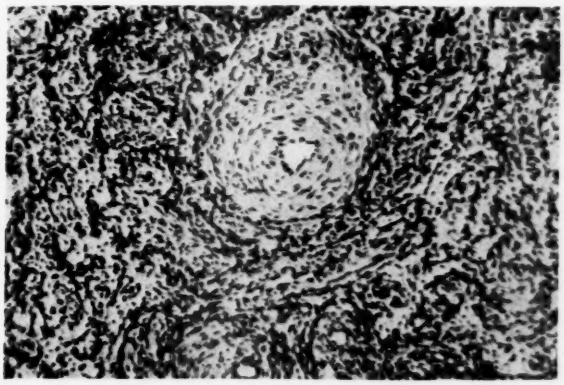

Fig. 6.—(Tumor 2.) In places the stroma is compact, elsewhere it is loose (×70). (Photographed by Clarence B. Mitchell.)

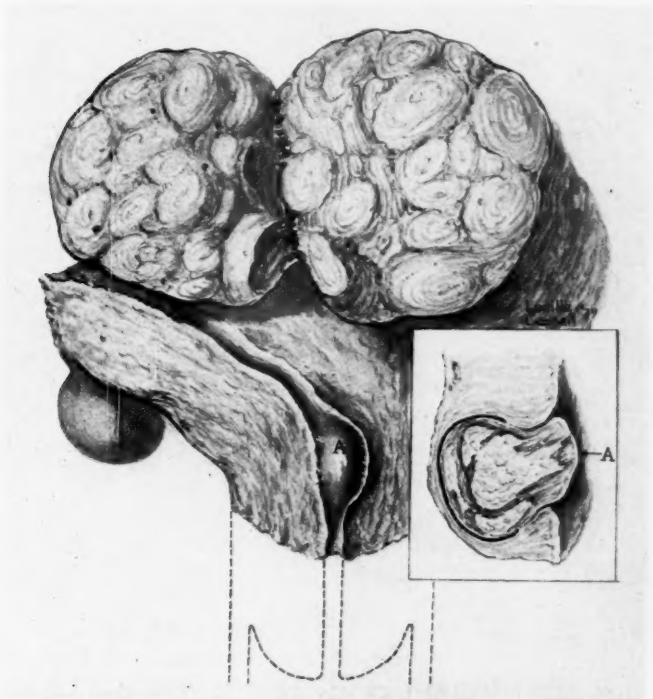

Fig. 7.—(Tumor 3.) Drawing of the opened gross specimen; the uterus had been amputated through the cervix. The tumors in the fundus were typical fibromyomas. At "*A*," a firm sessile intramural tumor bulged anteriorly into the canal, near the internal os. The insert is a vertical section of this tumor. Note the streaks of degeneration in it. Note, also, the capsule only over its posterior aspect. (Photographed by Clarence B. Mitchell.)

it was solid, ivory in color, and through it there were streaks of gray gelatinous-like material. Although there was a well-defined capsule posteriorly, this tumor invaded the uterine canal anteriorly, as a button-like, firm, sessile polyp.

Microscopically the tumors in the fundus were typical fibromyomas. The small tumor, that had become submucous, was devoid of a capsule on its mucosal margin (see Fig. 7). It was partially degenerated; there were areas of hyaline change and some of liquefaction. In places one recognized the classical architecture of a fibromyoma but, for the most part, typical cell bundles were absent. The tumor contained many arteries (see Fig. 8), i.e., large ones, small ones, and some that were minute. In some areas the stromal cells were arranged loosely; in others they were compact (see Fig. 8). Some of the arteries had extremely thick walls and about them there was a suggestion of periarterial collars of tumor tissue. The stromal cells were essentially uniform in size; there were no mitoses.

The patient is well.

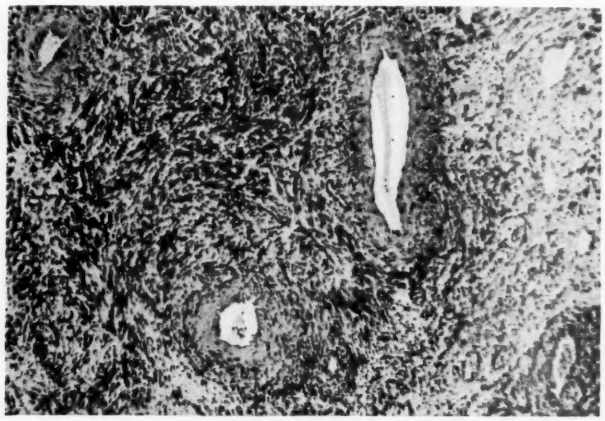

Fig. 8.—(Tumor 3.) The tumor contains many arteries. In some areas the stromal cells are arranged loosely (×52). (Photographed by Clarence B. Mitchell.)

DISCUSSION

It has been difficult to determine the nature of these tumors, and a careful survey of the literature has not helped materially in their classification. Furthermore there has been a lack of unanimity in the diagnoses suggested by others who have seen these sections. The most frequent reaction is to classify them as unusually vascular fibromyomas. Some believe that they are sarcomas; others consider them hemangiomas.

Although they are more vascular and more cellular than usual, for the following reasons these tumors are classified as fibromyomas: First, a fibromyoma is the most common solid uterine tumor; second, typical fibromyomas were also present in two of the three uteri; third, on gross examination, they appeared to be partially degenerated fibromyomas; fourth, a characteristic feature of their microscopic appearance is the paucity, but not complete absence, of usual fibromyoma architecture (each tumor contains some whorls of muscle fibers with bands of cells cut transversely, longitudinally and obliquely; Tumor 3 most closely approaches the usual microscopic appearance of a fibromyoma); fifth, one is accustomed to think of uterine fibromyomas as relatively avas-

cular tumors although it is recognized that there may be great variations in the number, and the size, of their intrinsic vessels. Consequently the ensuing discussion is an interpretation of the unusual microscopic picture found in these fibromyomas.

Each tumor contains areas of degeneration, either focal necrosis, small hemorrhagic zones, edema, liquefaction or hyaline changes. Consequently their vascularity and tendency to a compact stroma (see Fig. 8) may be relative, the result of compression and close packing of tissues; blood vessels and supporting fibrous tissue stroma might persist after intervening bands of smooth muscle fibers had degenerated and disappeared. I doubt that this is the sole explanation for their vascularity because the vessels are larger and more numerous than one usually finds in a fibromyoma, irrespective of its size, location, and the amount of degeneration in it.

The vascularity of a tumor would be altered if there had been interference with its blood supply, e.g., torsion of the pedicle. Neither one of the polypoid tumors was engorged or bloody; they were pale and edematous. Their vessels are normal arteries (see Fig. 5), not distended veins.

In the literature one finds comments on the increased vascularity sometimes encountered in the dependent portions of submucous fibroids. In the specimens under consideration, the increase in arteries is a diffuse phenomenon; it is not restricted to one portion of the tumors.

Sampson's observations on injected uteri are an excellent source of information about the great variations which may occur in the intrinsic vessels of uterine fibromyomas. He found that the vascularity of myomas differs markedly from that of the myometrium; frequently the tumors have more arterial supply but always fewer veins than the uterine musculature in which they are located. In some of his tumors there was extensive development of the intrinsic blood vessels, filled with the arterial injection mass, so that the injected specimen grossly appeared more like "an arterial angioma rather than a myoma." Sampson did not include either microscopic descriptions or photomicrographs in his contributions.

There are facts to support the contention that these tumors had already become sarcomatous, e.g., first, none of them is well encapsulated although in Tumor 3 a capsule is lacking only on the mucosal surface (see Fig. 7), and a capsule would not be expected around polypoid submucous fibroids; second, there is a richly cellular stroma in certain areas of Tumors 2 and 3; third, a few mitotic figures are present in Tumors 1 and 2 (more than an occasional mitosis is needed for the diagnosis of sarcoma. These mitoses are significant. They denote a tendency to rapid growth of tissue); fourth, the St. Luke's patient eventually died of sarcoma. However, there was a long interval, four and one-half years, between the vaginal removal of Tumor 1 and the hysterectomy, when sarcoma was found in the uterus.

Sarcomas are vascular tumors, but it is not typical for them to contain innumerable large normally developed arteries. Great difficulty may be encountered in making the microscopic diagnosis of sarcomatous

changes in a fibromyoma. The task is simplified when the tumor is soft, brainlike, partly necrotic and partly hemorrhagic and contains classical microscopic evidence such as abnormal mesoblastic cells, polymorphism, hyperchromatism and mitotic figures; giant cells are not uncommon. Variations in the histologic criteria, for the diagnosis of sarcoma arising in a uterine fibromyoma, are undoubtedly responsible for the discrepancies which have occurred in the incidence of sarcoma reported by different clinics.

The periarterial collars of tumor cells, so conspicuous in Tumor 1 (see Figs. 1 and 2), suggest that perithelioma might be an appropriate diagnosis. The term perithelioma is not generally accepted today, although it is permissible to speak of a peritheliomatous distribution of tumor cells. MacCallum has expressed the attitude of most pathologists as follows: ". . . . there often occurs what seems to be a local necrosis of the tumor cells from lack of sufficient blood supply. This leads to a curious condition in which only those cells which are close to the blood vessels remain alive. . . . Consequently the tumor appears to be made up of blood vessels each with a thick mantle of cells, and such tumors have been described as a separate type under the name angiosarcoma. The cells about the blood vessels have been regarded as arising from a hypothetical tissue spoken of as perithelium, and the tumor, therefore, called a perithelial angiosarcoma. It is possible that tumors with this structure really exist to which the explanation just given will not apply, but I have not seen them."

Tumor 1 appears to be lobulated (see Fig. 1). Each unit consists of an artery surrounded by a wide zone of tumor cells. Individual lobules are demarcated by a zone of necrosis (see Fig. 2). This tumor's structure coincides with MacCallum's description; consequently the terms perithelioma and angiosarcoma can be eliminated from further consideration.

One might think that these tumors are hemangiomas in uterine fibroids. Hemangiomas of the uterus are rare; they have been reported in the literature under the titles of angiomyoma, angiofibroma, hemangioma, hemangiomyofibroma, telangiectatic fibromyoma and hemangiectatic myoma. No illustrations have been found that are identical with the tumors which I have described; however, those which most closely resemble these specimens appear in the reports of angiomas of the uterus.

By definition, a hemangioma is a tumor composed of blood channels; these channels may be dilated capillaries, as in a telangiectasis, or large irregular blood spaces, as in a cavernous hemangioma. There may be proliferation of the intima lining the blood channels. Furthermore, one is likely to think of hemangiomas as tumors of veins although arteries too may participate. Grossly, a hemangioma is a bloody, purple red, vascular tumor; the specimens which I have described were pale, white, and partially degenerated. Furthermore, the blood vessels in these tumors are well-developed arteries of various sizes (not dilated capillaries and blood spaces); most of the arteries possess a delicate intimal lining and a thick muscular media. Consequently these tumors are not true hemangiomas.

A quotation from the Chapter on Angioma in Ewing's *Neoplastic Diseases* supplies a term which would distinguish these tumors from other fibromyomas. "Excessive development of blood vessels occurs in many tumors. . . . Very often such vessels present a normal or nearly normal structure and do not exhibit neoplastic growth. Such tumors are not true angiomas, but their vascularity may be indicated by the term 'angiomatosum.'" An abundance of normally developed arteries (see Fig. 5) constitutes the most striking microscopic characteristic of the tumors which I have described. Consequently fibromyoma angiomatosum is an appropriate name for them.

SUMMARY

An interpretation has been presented for the unusual histologic structure encountered in three, similar, uterine tumors. The microscopic findings include (1) innumerable well-formed arteries, (2) paucity of the usual architecture of a fibromyoma, (3) areas of degeneration, and (4) some tendency to compactness of the cellular stroma. These tumors were submucous; two were polypoid; and the other one lacked a capsule on its mucosal surface. A few mitotic figures have been found in two of the tumors. One shows striking periarterial distribution of tumor cells; this patient eventually died of sarcomatosis. The other patients are reported to be well, one and one-half and two and one-half years, respectively, after operation.

CONCLUSIONS

This is an unusual type of uterine fibromyoma. It appears to be potentially malignant; at any rate the patient from whom the first tumor was removed died of sarcomatosis. Myomectomy, alone, does not seem to be adequate treatment; the uterus should be removed. An appropriate name would serve to distinguish this tumor from other fibromyomas; it could be termed a fibromyoma angiomatosum.

REFERENCES

(1) *Barbour, A. H. F.:* J. Obst. & Gynaec. Brit. Emp. **24:** 61, 1913. (2) *Barbour, A. H. F., and Watson, B. P.:* J. Obst. & Gynaec. Brit. Emp. **20:** 116, 1911. Idem: Gynecological Diagnosis and Pathology, Edinburgh, 1922, W. Green and Son. (3) *Bell, W. B., and Clarke, H. H.:* J. Obst. & Gynaec. Brit. Emp. **9:** 348, 1906. (4) *Brenner, M.:* Zentralbl. f. Gynäk. **58:** 129, 1934. (5) *Clark, J. G.:* Bull. Johns Hopkins Hosp. **10:** 11, 1899. (6) *Curtis, A. H.:* A Textbook of Gynecology, ed. 3, Philadelphia, 1938, W. B. Saunders Co. (7) *Doran, A. H. G., and Lockyer, C.:* J. Obst. & Gynaec. Brit. Emp. **14:** 320, 1908. (8) *Dorland, W. A. N.:* Surg. Gynec. Obst. **23:** 576, 1916. (9) *Eiserth, P.:* Centralbl. f. allg. Path. u. path. Anat. **41:** 196, 1934. (10) *Ewing, J.:* Neoplastic Diseases, ed. 3, Philadelphia, 1928, W. B. Saunders Co. (11) *Frank R. T.:* Gynecological and Obstetrical Pathology, ed. 2, New York, 1931, D. Appleton-Century Co. (12) *Horgan, E.:* Surg. Gynec. Obst. **50:** 990, 1930. (13) *Johns, J.:* J. Michigan M. Soc. **32:** 504, 1933. (14) *Kelly, H. A., and Cullen, T. S.:* Myomata of the Uterus, Philadelphia, 1909, W. B. Saunders Co. (15) *Kimbrough, R. A.:* Am. J. Obst. & Gynec. **28:** 723, 1934. (16) *Leith, R. F. C.:* J. Obst. & Gynaec. Brit. Emp. **19:** 447, 1911. (17) *Lockyer, C.:* Fibroids and Allied Tumours, London, 1918, The Macmillan Co. (18) *MacCallum, W. G.:* A Textbook of Pathology, ed. 6, Philadelphia, 1936, W. B. Saunders Co. (19) *Neumann, H. O.:* Arch. f. Gynäk. **139:** 161, 1930. (20) *Novak, E., and Anderson, D. F.:* Am. J. Obst. & Gynec. **34:** 740, 1937. (21) *Orsos, F.:* Zentralbl. f. Gynäk. **58:** 122, 1934. (22) *Pusch, L. C.:* Am. J. Obst. & Gynec. **24:** 907, 1932. (23) *Rutten, E.:* Frankfurt. Ztschr. f. Path. **46:** 151, 1934. (24) *Sampson, J. A.:*

Surg. Gynec. Obst. **14**: 215, 1912; **16**: 144, 1913. (25) *Schumann, E. A.:* Other Tumors of the Uterus, Curtis' Obstetrics and Gynecology, **2**: Philadelphia, 1933, W. B. Saunders Co. (26) *Veit-Stoeckel:* Handbuch der Gynäkologie, **6**: Part 1, München, 1930, J. F. Bergmann. (27) *Watson, B. P.:* Am. J. Obst. **69**: 806, 1914. (28) *Wright, F. W.:* Surg. Gynec. Obst. **43**: 282, 1926.

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DISCUSSION

DR. BENJAMIN P. WATSON, New York, N. Y.—As long ago as 1911 I published, with the late Dr. A. H. F. Barbour, two cases of what we then called perithelioma, one of the uterus and one of the tube. As Dr. Gardner has said, this term, perithelioma, is no longer admissible, but the tumors as then described were very similar in gross and in microscopic appearance to those presented today.

Dr. Gardner was so good as to send me the original microscopic preparations from his cases. I was so struck by them that I asked Dr. Arthur Purdy Stout, head of the Surgical Pathological Laboratory of the Columbia University College of Physicians and Surgeons, to go over them with me. I should like to quote Dr. Stout's commentary:

"I have spent some time studying the tumor of the uterus sent to you by Dr. George H. Gardner, which he proposes to call 'Fibromyoma angiomatosum.' It is a most interesting lesion, and I think that we can get some clue to its origin from the section No. 3072 of the original growth which presented in the external os and was removed by cutting its pedicle in 1931. This tumor resembles in many respects a tumor which grows in the skin and subcutaneous tissue, coming from the smooth muscle of the blood vessels. There are other smooth muscle tumors in the skin which come from the hair muscles and the muscles of the genital zones, such as the nipple, areola, and vulva. These are composed exclusively of smooth muscle, but the ones that come from the vessels are also well supplied with large, thick-walled vessels not unlike the ones in the cervical tumor. I think, therefore, that I would call this original tumor a leiomyoma of vascular type. I think that Dr. Gardner is in error in calling the vessels arteries. Just because a vessel has thick muscle walls does not necessarily make it an artery. Differential stains should be done to show the actual distribution of smooth muscle, elastic tissue and connective tissue in order to determine the nature of these vessels. To me they seem much more like thick-walled veins.

"I think that he is probably right in believing that the malignant portion of the growth is a leiomyosarcoma, but it is a great pity not to attempt to get confirmation of this by differential stains. It is of very great interest to find that the tumor, even in its malignant manifestations, still continues to form large vessels."

Dr. Stout has made a special study of these leiomyomas which originate in the smooth muscle of blood vessel walls and tend to occur in the subcutaneous tissues in various regions of the body. He is inclined to think that the tumors described by Dr. Gardner are of essentially the same nature. On the other hand we have always been inclined to think that fibromyomas of the uterus are avascular tumors. As Dr. Stout says in his criticism, the thick-walled vessels are not necessarily arteries, most of them are veins.

After seeing Dr. Gardner's specimens I took at random a number of sections of ordinary fibroid tumors of the uterus to see what type of blood vessels they contained and was rather surprised to find that a great many of those ordinary fibroids had large vessels very much the same as those which Dr. Gardner found in his tumor. It seems entirely possible that the tumor described by Dr. Gardner took origin in the smooth muscle of such vessel walls.

Dr. Stout's suggestion that the tumor be classed as a leiomyoma of vascular type seems to me to fit the picture better than the name suggested by Dr. Gardner. I feel certain, now that attention has been drawn to this tumor, that many more will be described and that agreement will be reached regarding its proper classification.

The important thing clinically is a recognition of the fact that sarcomatous change is a very definite possibility and that, as Dr. Gardner states, avulsion of those growths, when presenting at the cervix, or their removal from the uterine wall by myomectomy is not sufficient; a hysterectomy ought to be done.

DR. EMIL NOVAK, BALTIMORE, MD.—On the basis of these photomicrographs which Dr. Gardner has shown and the history of the patients, I feel that all three of these cases are sarcomas of the uterus. Both myomas and sarcomas differ very much in the matter of blood supply, as well as in the distribution of lymph vessels. The latter, for example, are sometimes extremely large and numerous. In the benign myoma the blood supply is ordinarily not a very rich one. Little is known as to the etiology of myoma, although most pathologists feel that the origin is from certain so-called indifferent cells, rather than from the fully formed, mature, involuntary muscle cells of the uterus.

Many of you will remember the term "recurrent myoma" of the uterus, which was not infrequently found in the older literature. It referred to a group of tumors, histologically apparently benign, which recurred after removal. For example, in such a case reported some years ago from Halban's Clinic, a complete operation was done for a myoma which histologically was benign. Several recurrences necessitated repeated operation, and it was only after the last operation that sarcoma was demonstrated microscopically. It must, however, have been present in potential form long before this.

While the finding of mitoses is of great importance in the diagnosis of sarcoma, one frequently finds in cases of undoubted sarcoma many areas in which there is no mitosis whatsoever. In some sarcomas, there is a tendency to the perivascular arrangement of the sarcoma cells, constituting the type spoken of as angiosarcoma. However, this appearance is often due to the fact that the extensive degeneration which involves most parts of the tumor spares the cells immediately around the blood vessels.

Finally, one of Dr. Gardner's cases illustrates the fact that when one finds large, bulky, friable polypoid growths of the endometrium or cervical mucosa one should always suspect the existence of sarcoma. Sarcoma originating in the uterine mucosa always has a tendency to assume this polypoid form, although there is also extensive invasion of the entire uterine wall.

DR. GARDNER (closing).—I think it has been proved that the vessels in these tumors are arteries. In differential stains the relative amount of smooth muscle tissue and connective tissue varies a great deal. Some of the vessels possess these tissues in equal amounts; however in most of them the smooth muscle fibers predominate, a ratio of three or four to one. These vessels are composed of a delicate intima, a thick muscular media and a fibrous tissue adventitia. Furthermore, many have both an external and an internal elastic membrane although in some vessels in the first tumor, the elastic tissue is a very delicate structure.

In several respects these tumors differ strikingly from those described by Dr. Stout. In his leiomyomas of vascular origin arising in the skin, none of the vessels possessed an internal elastic membrane. Furthermore, in many places Dr. Stout found continuity between the smooth muscle fibers of the vessel wall and the tumor itself. Differential stains show that there is a well-defined connective tissue adventitia between the smooth muscle fibers of the vessels and the stroma of the tumors which I have described.

I can understand Dr. Novak's attitude, viz., that these tumors might be sarcomas. I have cited the observations which led me to classify them as benign tumors, although they appear to be potentially malignant.

ENDOMETRIOSIS OF THE LUNGS*

An Experimental and Clinical Study

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ENDOMETRIOSIS is such a commonplace disease, and it has been so often and thoroughly discussed we would feel apologetic were it not for the fact that we have a new aspect of the subject for presentation. We shall, therefore, limit our consideration of its development to those points that are relevant to our problem of endometriosis of the lungs.

Rokitansky, in 1860, first described this lesion as an adenomyoma of the uterine wall. V. Recklinghausen renewed interest in the subject in his publications from 1893 to 1896, in which he ascribed the origin of the heterotopic endometrium in the uterine wall to the development of embryonic rests of the Wolffian ducts. In 1896, Cullen made his first contribution to the subject in describing an adenomyoma of the round ligament. He was the first to show that misplaced endometrial tissue in the uterine wall may be the result of direct invasive growth of the endometrium. In 1899, W. W. Russel was the first to describe endometrial tissue in the ovary, the so-called "chocolate cyst." Koch in 1911, Schwarz, Norris and Cassler in 1919, and Cullen in 1920, described endometrial tissue in the ovary. In 1920, Sampson made his original contribution in which he analyzed 23 cases; the total number on record at that time was less than 20. Since then a voluminous literature has sprung up on the subject. The lesion has been found in a diversity of locations including: vulva, perineum, vagina, urinary bladder, uterus, round, broad, and sacrouterine ligaments, tubes, ovaries, rectovaginal septum, intestines, umbilicus, laparotomy scars, lymph nodes (inguinal, and iliac), thigh, and brachioradialis muscle.

Endometrial tissue has been successfully transplanted to numerous organs in laboratory animals, including the anterior chamber of the eye. The theories which have been promulgated to explain the diversity of endometrial transplants are familiar, namely: Congenital theory, mucosal invasion theory (endometrium and endosalpinx), serosal theory, Sampson's tubal regurgitation theory, and metastatic theory.

For several years it has seemed probable that endometrial tissue might become implanted in the lungs.

This suspicion was based on several known facts: (1) Halban and Sampson have demonstrated endometrial tissue in the lumina of veins and lymphatics. We have sections in our laboratory to show this mode of transportation. Additional support to the fact that endometrial tissue is transported in this way is offered by finding endometrium in the inguinal and iliac lymph glands. Several cases of inguinal implants have been described. Taussig has found that about 10 per cent of the cases in which he has done lymph gland resections for cervix uteri cancer will show endometrial tissue in the iliac glands; (2) normal syncytial tissue and chorionepithelioma are transported to the lungs through the blood stream; (3) the

*Read, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Association, The Seigniory Club, Que., June 17 to 19, 1940.

only plausible explanation for finding endometrial tissue in such locations as the brachioradialis muscle (Navratil and Kramer) and thigh (Mankin) is that it must get into the systemic circulation; and (4) the diversity of tissues in which endometrial implants have been found would indicate the lungs are not resistant to its growth. In an attempt to confirm this suspicion, with the encouragement of our Chief, Dr. Otto H. Schwarz, we decided to do some experimentation.

METHOD

Obviously, our first problem was to implant the endometrium of a laboratory animal into the lungs and to note whether it would grow. We realized the use of large rabbits (2,000 Gm. or over) would be advantageous for two reasons. In the first place, the uterus and horns are quite large, facilitating the removal of the mucosa; and in the second place, we conceived the idea of injecting the tissue into the ear vein, a very simple procedure. We could thereby simulate the transportation of tissue through the uterine veins and also be assured of wide dissemination of the tissue throughout the lungs. Our mortality dropped to zero when we stopped doing hysterectomies and only did hysterotomies for removal of the mucosal clippings. The horn was closed with a running suture of silk. Very little trauma and no shock attended this procedure. In the last 15 operations with improved technique, only one animal died as a direct result of the operation, and this was attributed to the anesthesia.

Previous to the operation theelin in oil was given in order to stimulate growth of the endometrium and thereby facilitate the removal of the tissue. The clippings suspended in normal saline were injected into the ear vein through an 18 gauge needle. After the injection the vein was thoroughly washed with normal saline solution. It was astonishing what large pieces of mucosa could be injected without being fatal to the animal.

Table I shows a résumé of this experiment.

TABLE I. ENDOMETRIOSIS OF LUNGS

RABBIT	THEELIN (2,000 U.)	ENDOMETRIUM IMPLANTED	KILLED	DIED	ENDOMETRIUM IN LUNGS
1980	1/22/38	1/24/38	4/16/38		None
1981	1/22/38	1/24/38	4/16/38		Stroma
1944	1/28/38	1/31/38		3/22/38	Stroma (?) and fragmented epithelium (?)
A-6	2/ 4/38	2/ 7/38	4/16/38		None
A-7	2/ 8/38	2/10/38		3/15/38	Glands
A-8	2/12/38	2/15/38		3/ 8/38	None
A-9	2/12/38	2/15/38		3/ 6/38	Stroma and glands
A-10	2/20/38	2/23/38		4/ 2/38	Glands
A-19	2/20/38	2/23/38		4/ 4/38	"Chocolate cyst," stroma and glands
A-23	2/26/38	2/28/38		4/15/38	Glands
A-537	11/26/39	11/27/39	4/30/40		Stroma and glands
A-538	11/26/39	11/27/39	4/30/40		None

Summary: Out of 12 rabbits operated, 8 showed endometrial implants.

Control: The lungs of 10 normal rabbits were examined for endometrial tissue and none was demonstrated.

The accompanying photomicrographs, Figs. 1 to 6 inclusive, give a visual picture of the development of the pulmonary implants.

With this phase completed, the next problem attempted was to impregnate some of the animals which had been previously given endometrial implants in the lungs to see if a decidual reaction would occur. In pregnant women, ectopic endometrial tissue may undergo decidual

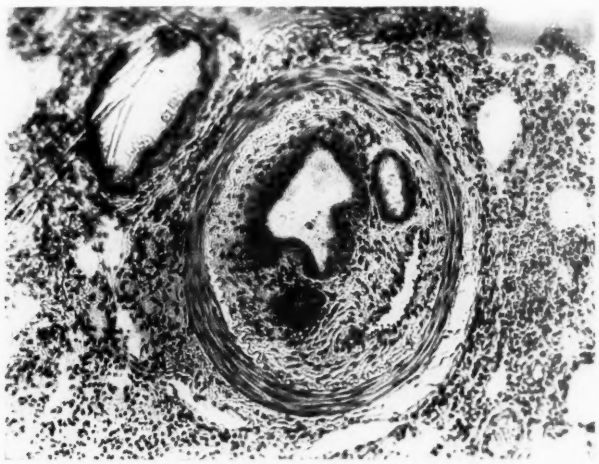

Fig. 1.—The endometrial tissue has proliferated and almost obliterated the lumen of the vein.

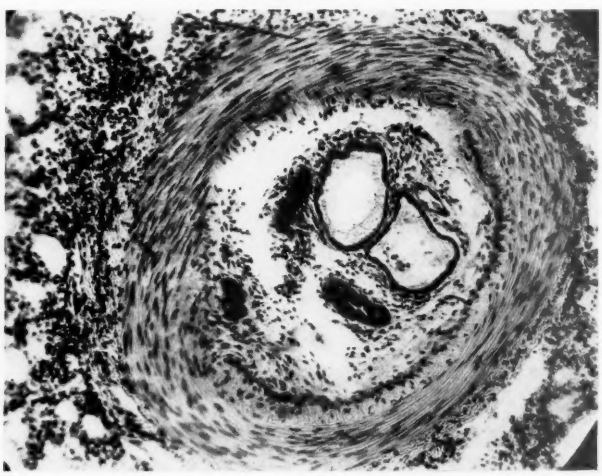

Fig. 2.—The lumen of an artery has been obliterated.

formation. Several years ago Loeb proved, and his work has been confirmed, that if the horn of a guinea pig or rabbit is tied off and the animal becomes pregnant, a decidual reaction will not occur in the sterile horn unless the mucosa is traumatized in some manner such as incising, passing of a suture, etc. Therefore, it was with some misgiving that we undertook this experiment.

Table II gives a composite picture of this experiment.

The photomicrographs, Figs. 7 to 9 inclusive, demonstrate unequivocally the development of a decidual reaction in the lung implants. The trauma, if present, that was necessary to produce the decidual reaction in the pulmonary implants was problematical.

Fig. 3.—The wall of this vein has been disrupted in two places.

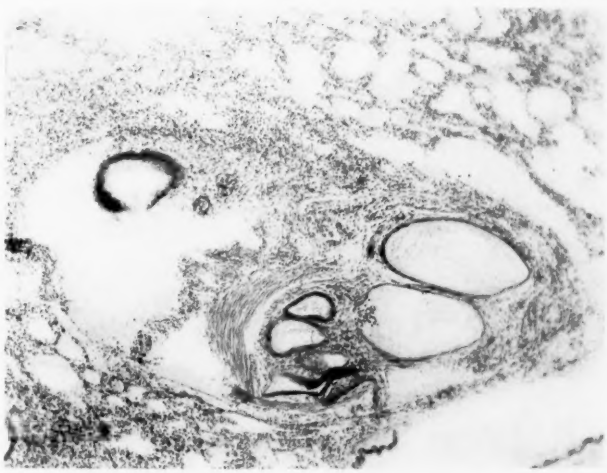

Fig. 4.—Only a fragment of the vein wall remains. The endometrial tissue is invading the parenchyma of the lung.

The next problem attacked was to demonstrate the effect of an estrogenic hormone on the implanted tissue. One should expect hyperplastic changes in both the glands and stroma with prolonged administration of this hormone in large doses. Table III presents the data on this experiment.

TABLE II. ENDOMETRIOSIS OF LUNGS PLUS PREGNANCY

RABBIT	THEELIN (2,000 U.)	ENDOMETRIUM IMPLANTED	BRED	KILLED	DIED	RESULTS
A-305	7/17/39	7/19/39	8/27/39	9/20/39		Uterus: Pregnant both horns Lungs: Diffuse glands and decidua
A-307	7/24/39	7/26/39	9/19/39	10/11/39		Uterus: Pregnant, unoperated horn Lungs: Glands and decidua
A-308	7/24/39	7/26/39	10/ 8/39	10/30/39		Uterus: Pregnant, unoperated horn Lungs: Glands and decidua
A-545	11/30/39	12/ 1/39	1/30/40		2/12/40	Uterus: Enlarged and succulent, decidua? Lungs: Glands, no decidua. Miscarriage?
A-546	11/30/39	12/ 1/39	1/30/40	2/23/40		Uterus: No evidence of pregnancy Lungs: Glands, decidua?
A-592	12/14/39	12/18/39	1/30/40	2/23/40		Uterus: Pregnant both horns Lungs: Glands and decidua

Control: The lungs of 10 normally pregnant rabbits were examined for trophoblast or decidua and none was found.

TABLE III. ENDOMETRIOSIS OF LUNGS PLUS STILBESTROL

RABBIT	THEELIN (2,000 U.)	ENDOMETRIUM IMPLANTED	DIED	KILLED	STILBESTROL	RESULTS
A-539	11/26/39	11/29/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Endometrium thin
A-540	11/26/39	11/29/39		4/30/40	Given*	Lungs: One small area of stroma in blood vessel Uterus: Endometrium very thin
A-547	11/30/39	12/ 1/39	12/ 1/39	Anesthesia		
A-589	12/14/39	12/18/39	3/23/40		Given*	Lungs: Diffuse endometriosis Uterus: Endometrium thin, very few glands
A-590	12/14/39	12/18/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Necrotic, no epithelium
A-591	12/14/39	12/18/39		4/30/40	Given*	Lungs: Endometriosis Uterus: Necrosis of endometrium and myometrium

Control: Animals reported in Table I serve as controls.

*Rabbits were given 1 mg. of stilbestrol 3 times a week from 1/30/40 to 4/16/40 (77 days); then 2 mg. 3 times a week for 7 days, and finally, 5 mg. daily for 5 days. All received a total of 64 mg., except No. A-589, which received 22 mg.

The photomicrograph, Fig. 10, demonstrates the effectiveness of stilbestrol* in this experiment. It is especially interesting to note that Rabbit A-589, which had about one-third the total dosage administered in a little over one-half the time, showed diffuse endometriosis of the lungs complicated by empyema from which it apparently died. Those

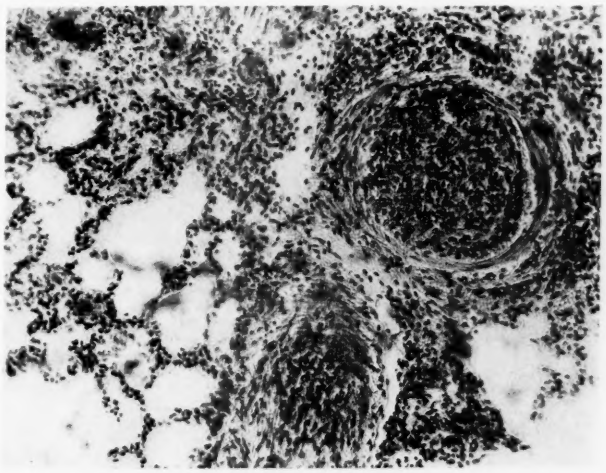

Fig. 5.—Two veins filled with endometrial stroma.

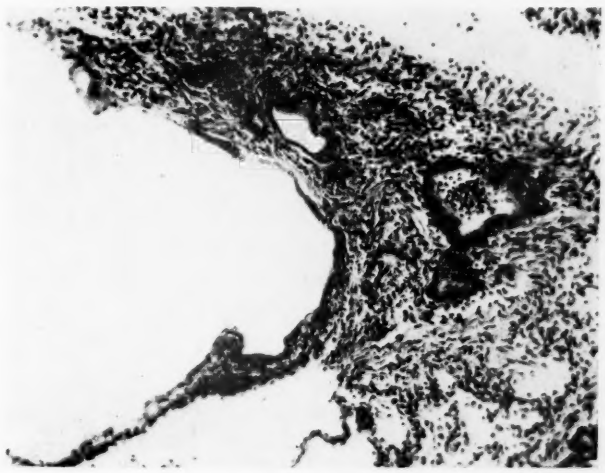

Fig. 6.—A microscopic section through the cyst wall showing typical endometrial tissue.

receiving larger doses over a longer period of time showed very little or no endometrial tissue in the lungs. Also the uteri showed inactive mucosae and necrosis in some cases. It is a known fact that excessive doses of stilbestrol will produce necrosis of the rabbit's uterus. It may be possible that large doses suppress the anterior pituitary which in

*We wish to express our appreciation to Eli Lilly and Company, Indianapolis, Indiana, for the generous supply of stilbestrol and for their interest in this experimental work.

turn inhibits or diminishes ovarian activity, so that there is a lack of estrone stimulation to the endometrium. We are making further experiments to demonstrate the effect of estrogenic hormones in graduated doses on normal and aberrant endometrial tissue.

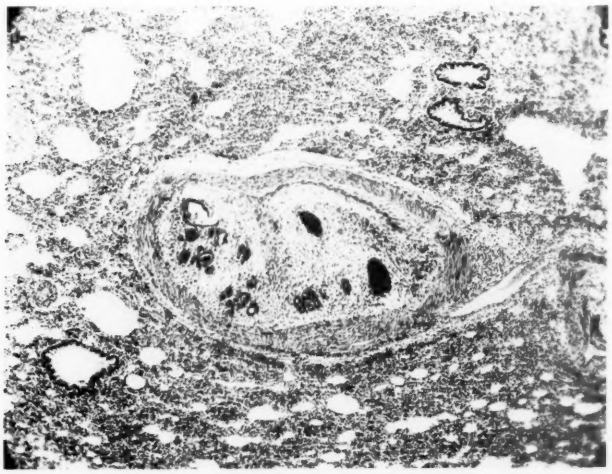

Fig. 7.—The endometrial stroma in this vein has undergone decidual formation.

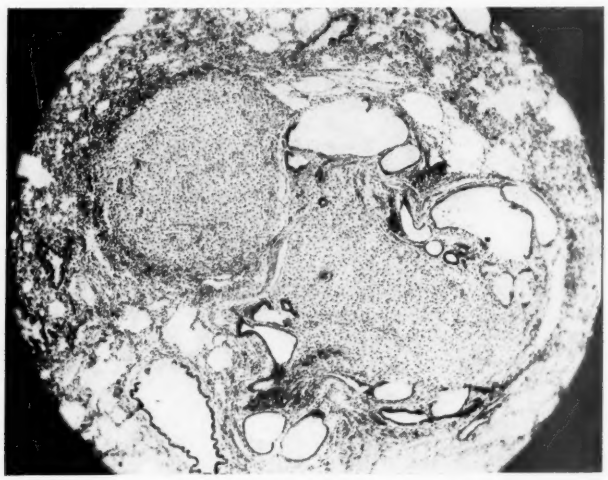

Fig. 8.—A diffuse decidual reaction.

We believe this work is not only of didactic interest but is of considerable practical importance. The theoretical possibilities are obvious. We have attempted to demonstrate some of these possibilities in fact.

DISCUSSION

In the first place, we are of the opinion that vicarious menstruation is due to an endometrial transplant in whatever region from which the

periodic discharge issues. These implants may reach the systemic circulation either through a patent foramen ovale or propagate through the capillaries of the lungs and reach the left heart. How else could such tissue reach the arm and thigh? With this possibility in mind, we have made every effort to obtain tissue from women having vicarious menstruation, but to date have not succeeded. We have observed three women

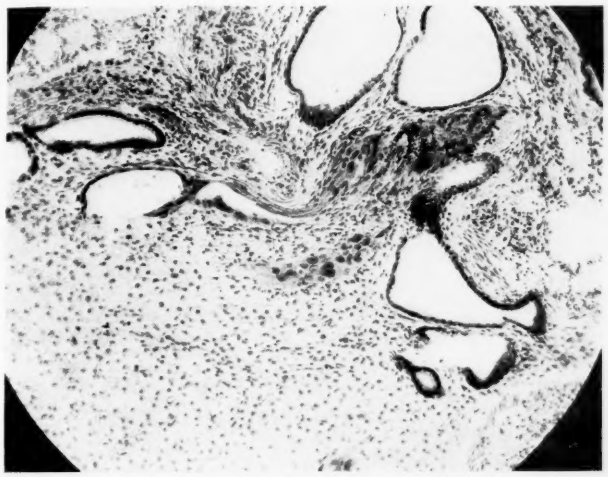

Fig. 9.—A high-power photomicrograph of a portion of Fig. 8, showing characteristic decidual cells and epithelial plasmodia.

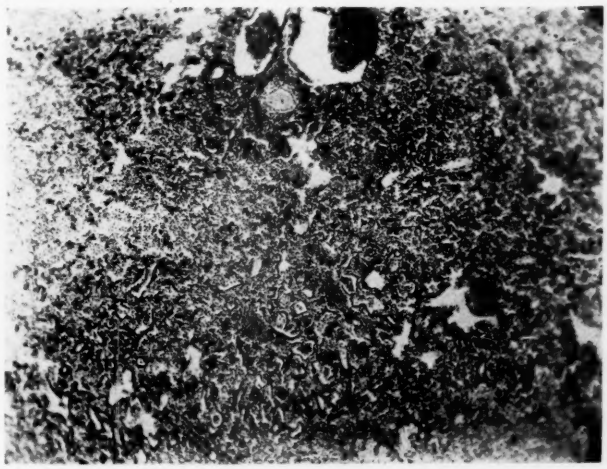

Fig. 10.—A low-power photomicrograph through the lung of A-589, showing widespread gland and stromal proliferation.

who have or have had vicarious menstruation, and although we have not been able to demonstrate ectopic endometrium in the area from which the blood came, the history and physical findings are presumptuous.

The first patient showed endometriosis of the inguinal lymph nodes and hemoptysis at each menstrual period. The hemoptysis stopped following deep x-ray therapy to the ovaries. After five months

the hemoptysis recurred for a few months and has not returned now for over two and one-half years. The other two patients have histories and physical signs characteristic of pelvic endometriosis. Each has hemoptysis at the menstrual period. The fact that the hemoptysis occurred simultaneously with the development of the pelvic endometriosis, is suggestive of an endometrial implant in the lungs.

Another practical consideration is that of tumor formation in the lungs. This may be a source of some of the primary benign and malignant tumors in the lungs of women. Our experiments have demonstrated that the aberrant endometrium may be localized or grow in a diffuse manner. Misplaced endometrial tissue has the same potentiality of malignant development as has normal endometrium. In fact, it possesses two characteristics of malignant cells. First, it is invasive, and second, it will live and proliferate in a foreign host. Statements are made that it is rare for ectopic endometrium to become malignant.

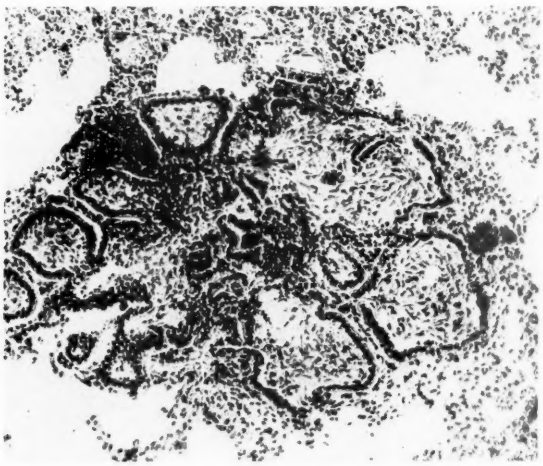

Fig. 11.—Papillary growth of endometrium in the lung.

We wonder whether that statement is correct. Can it be that this tissue is not always recognized as a result of changes in morphology and location? It would seem that this tissue has a greater potentiality for malignant development by virtue of the fact that it has the "growth urge" even in an alien tissue. It is well known that some adenocarcinomas of the ovaries arise from endometrial implants. The papillary serous cystadenomas may arise from the same source. Fig. 11 shows a papillary growth of this tissue in the lung. Added evidence to support this theory that papillary serous cystadenomas arise from Müllerian derivatives can be demonstrated in the human ovary. We have sections in our laboratory to show the development of the germinal epithelium of the ovary into tissue that morphologically simulates endometrial tissue. In many areas this tissue grows in a papillary formation. Through the courtesy of Dr. Evarts A. Graham, we have had the opportunity

to make a microscopic study of 33 primary lung tumors removed from women. We were not able to demonstrate endometrial tissue in any of these cases.

Finally, if endometrial tissue does occur in the lungs, it is conceivable that hemoptysis and roentgenograms may lead one to suspect tuberculosis. In many cases of suspected tuberculosis, tubercle bacilli cannot be demonstrated. It seems quite likely that a diffuse or circumscribed lesion in the lungs would produce a picture that might be mistaken for tuberculosis. We urge the roentgenologist, internist, and chest surgeon to keep this possibility in mind.

The fact that the lesion has not been demonstrated in the lungs does not necessarily mean that it does not exist nor that it is not frequent. For example, endometriosis of the pelvis was not recognized with any frequency until Sampson's report in 1920. Now we know the lesion is present in about 10 per cent of adult women. Banting and Best called attention to the lesion of the islands of Langerhans in diabetes mellitus. The lesion has always been there, but it was not recognized. Many other examples showing the fallacy of the argument that because a lesion has not been found it does not exist, might be enumerated.

CONCLUSIONS

1. Endometrial tissue can be transported through veins.

2. Endometrium of the rabbit can be transported through the veins to the lungs where it will remain viable and invade the parenchyma.

3. Implants of uterine and horn mucosa in the lungs may undergo decidual formation if the animal becomes pregnant.

4. An estrogenic hormone (stilbestrol) in relatively large doses apparently stimulates the endometrial tissue implanted in the lungs. Excessively large doses may inhibit the growth of this tissue.

5. Clinical evidence correlated with experimental work leads us to the following deductions:

a. Vicarious menstruation is a result of an endometrial implant in whatever region from which the periodic bloody discharge issues.

b. Certain benign and malignant tumors in the lungs of women may arise from endometrial transplants.

c. Pulmonary endometrial implants may be mistaken for tuberculosis.

REFERENCES

(1) *Halban, J.:* Wien. klin. Wchnschr. **37:** 1205, 1924. (2) *Hobbs, John E., and Bortnick, A. R.:* Surg. Gynec. Obst. **69:** 577, 1939. (3) *Jacobson, V. C.:* Arch. Surg. **5:** 281, 1922. (4) *Loeb, L.:* Proc. Soc. Exper. Biol. & Med. **1:** 93, 1903-1907. (5) *Idem:* Proc. Soc. Exper. Biol. & Med. **5:** 102, 1907-1909. (6) *Idem:* J. A. M. A. **50:** 1897, 1908. (7) *Mankin, Z. W.:* Arch. f. Gynäk. **159:** 671, 1935. (8) *Navratil, E., and Kramer, A.:* Klin. Wchnschr. **15:** 1765, 1936. (9) *Sampson, J. A.:* Am. J. Obst. & Gynec. **14:** 422, 1927. (10) *Idem:* Am. J. Path. **3:** 93, 1927. (11) *Seelig, M. G., and Hobbs, John E.:* Festschrift dedicated to Robert Tilden Frank, June, 1937, St. Louis, The C. V. Mosby Company, 1937. (12) *Taussig, F. J.:* Am. J. Obst. & Gynec. **36:** 819, 1938.

DISCUSSION

DR. ROBERT A. KIMBROUGH, JR., PHILADELPHIA, PA.—We have seen from Dr. Hobbs' slides that there is certainly histologic identification of the implants with endometriosis, and we must concede that he has been successful in transplanting endometrial tissue into the lung. Since Dr. Sampson demonstrated the presence of endometrial fragments in the venous sinuses of the uterus as long as eighteen years ago, it is perhaps surprising that so few instances of distant metastasis have been observed.

I would like therefore, to cite the following case as a possible example of endometriosis of the lung: Mrs. S. J., aged 43 years, para ii, consulted me on March 11, 1940 because of severe pain in the right posterior lower chest occurring synchronously with her two previous menstrual periods. On each occasion the pain was of three days' duration, and at the last period the pain was severe enough to require morphine for relief. Respiratory movements did not affect the intensity of the pain, and there was no hemoptysis or cough. In the intervals between these attacks she had had no discomfort whatsoever.

General physical examination revealed nothing of importance. There were no unusual auscultatory findings in the chest, and the pelvic organs were normal except for the presence of a small intramural uterine myoma. An x-ray study of the chest revealed nothing abnormal, and in particular no shadow over the area affected by the pain. Despite this negative study a tentative diagnosis of endometriosis of the lung was made and further observation was advised.

Unfortunately the patient's subsequent course has weakened my original opinion. She had one more attack of pain four or five days subsequent to her next period, and has recently had two menstrual periods attended by no recurrence of discomfort. Is it not possible, however, that three successive menstrual reactions in this heterotopic endometrium may have either temporarily or permanently destroyed its functional ability?

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Hobbs has clearly established the fact that endometrial tissue will grow in the lung, and that such ectopic tissue exhibits the same physiologic responsiveness as does the normal uterine mucosa. The important question is the applicability of this work to the general problem of the histogenesis of endometriosis.

In our own laboratory we have often seen emboli of endometrium in the veins and lymphatics, but there are few who accept Halban's theory of the lymphogenic etiology of pelvic endometriosis. The distribution of endometrium in the latter condition is not at all what would be expected if the lymphatic route of the dissemination were the important one.

In another section of his work Dr. Hobbs shows that his studies may possibly be applied to the explanation of vicarious menstruation, but on this point, as he himself states, the evidence is still very incomplete. I am inclined not to agree with him that the presence of actual endometrium is necessary for the occurrence of vicarious menstruation, as I think that such vicarious bleeding is readily explainable on the basis of certain vascular changes, such as increased fragility of the vessels, which have been shown to characterize the menstrual epoch. Furthermore, the recent studies of Collip and others have shown marked hyperemia of certain areas of the nasal mucosa in monkeys at the time of menstruation, and the frequent cases of vicarious nasal menstruation in women would seem to indicate that such vascular changes are probably sufficient to explain this phenomenon.

It would seem incredible that actual endometrial tissue is present in all cases of vicarious menstruation. For example, in a recent patient, in addition to nasal and rectal vicarious menstruation, large purple purpuric areas appeared on the lower extremities below the knee. While, therefore, Dr. Hobbs is to be complimented on his project of searching for endometrium in these cases of vicarious menstruation, I would be inclined to think that this search will not be successful.

DR. EDWARD ALLEN, CHICAGO, ILL.—With reference to a chocolate cyst in the lung, some years ago we injected large amounts of estrogenic substances into rabbits which previously had had implants of endometrial tissue in the eye. Sufficient hormone was given to produce a metaplasia of the endometrial cells and a change of the connective tissue into cells of typical decidual reaction. In none of these sections did we find any evidence of bleeding.

I would raise the question whether what Dr. Hobbs has described may be called a chocolate cyst in an animal that does not bleed from the endometrium. I would also question the statement that bleeding from the lung may be taken as evidence of ectopic tissue in cases where tuberculosis might be present. Hemoptysis is rather common at the time of the menstrual period in tuberculosis due to increased fragility of blood vessels.

DR. HOBBS (closing).—I think Dr. Novak will have to concede that endometrial tissue may be transported through the lymphatics and through the blood stream into the systemic circulation. How else can he explain the ectopic tissue found in the brachio-radialis muscle and in the thigh? Of course, I do not say that every vicarious menstruation has this basis, but we are hoping to demonstrate ectopic endometrial tissue in women having vicarious menstruation.

VITAMIN K IN OBSTETRICS*

A Review of One Year's Experience

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IT IS well known that the newborn infant exhibits an especial tendency to bleed. For example, the incidence of retinal hemorrhage during the first week of life ranges between 12 and 30 per cent,[1, 2] while bloody spinal fluid is demonstrable in one baby in ten at this period.[3] It is equally well known that this hemorrhagic tendency sometimes assumes pathologic proportions and gives rise not only to the syndrome of hemorrhagic disease, but in conjunction with trauma or anoxia, to cerebral bleeding, possibly the most common cause of neonatal death.

A rational explanation for this tendency of the newborn to bleed was advanced in 1937 by Brinkhous, Smith, and Warner,[4] who showed that the plasma prothrombin level of babies at birth is exceedingly low, ranging from 14 to 39 per cent of the usual adult value. These observations were subsequently confirmed by Moore and Javert,[5] as well as by Hellman and Shettles[6] in our clinic; the latter authors added the information that the plasma prothrombin concentrations of premature infants are extraordinarily low, averaging but 11 per cent of the adult figure. Of particular import is the fact that each of these groups of workers (Brinkhous, Smith, and Warner; Moore and Javert; Hellman and Shettles) included in their report a case of hemorrhagic disease, and in every instance the prothrombin level was the lowest encountered, namely, about 5 per cent of the adult value. Since authorities agree that plasma prothrombin is essential for clot formation and is, in all probability, the determining factor in the rate of blood coagulation, these observations place the etiology of hemorrhagic diatheses in the newborn on an intelligible basis.

From a practical viewpoint, of course, the importance of these findings hinged on the discovery of some substance capable of raising the low prothrombin levels of these infants, a need which was met by the discovery of Vitamin K by Dam in 1935, and its subsequent purification and synthesis by Almquist and Stoksted, Doisy and his associates, Fieser and his co-workers, Ansbacher, and a score of other investigators. Vitamin K is a fat-soluble substance, the absence of which in the diet of chickens causes the blood to become very slow in clotting, with the result that multiple hemorrhages develop; indeed, the blood from chickens fed on a vitamin K deficient diet will stand in the laboratory over night without clotting. Upon studying this blood, investigators have found that its poor clotting properties are ascribable to the fact that the normal amount of prothrombin is lacking. Upon administering vitamin K to such chickens, the plasma prothrombin is promptly raised, the clotting time accelerated, and the hemorrhagic diathesis cured. Vitamin K is

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found in a wide variety of foods, the richest sources being alfalfa, hog's liver, hemp seed, and decayed fish meal.

If low plasma prothrombin levels in experimental animals can be raised by the administration of vitamin K, it seemed reasonable to hope that similar results could be achieved in the newborn. To this end, work was begun in January of 1939, along two avenues of approach: (a) antenatal administration of vitamin K to the mother and (b) direct administration of vitamin K to the infant after birth. The results of these investigations have been published by Shettles, Delfs, and Hellman[7] and may be summarized as follows:

1. The plasma prothrombin level of the newborn infant can be raised severalfold by administering vitamin K to the mother antenatally, even when it is given as late as four hours before delivery (Tables I and II).

2. Although the feeding of vitamin K to the baby after birth also increases its prothrombin concentration, the levels so reached are not as high as those achieved by antenatal administration to the mother.

TABLE I.* THE PLASMA PROTHROMBIN LEVELS OF MOTHER AND CHILD, EXPRESSED IN DILUTION UNITS, IN THIRTY-ONE FULL-TERM DELIVERIES

NAME	RACE	INFANT WEIGHT	PROTHROMBIN DILUTION UNITS	
			MOTHER	INFANT
C. B.	W.	3,660	138.9	39.2
Z. B.	C.	2,825	202.9	13.7
R. B.	W.	4,010	201.2	33.8
E. B.†	W.	2,880	92.4	28.2
		2,800		26.8
N. B.	C.	3,305	157.0	41.3
N. B.	C.	3,600	45.0	14.0
M. C.	C.	4,075	99.0	36.5
M. C.	W.	3,120	45.8	14.8
N. E.	W.	3,290	130.6	26.8
B. F.	C.	2,465	237.6	60.4
M. G.	C.	2,535	173.2	32.2
J. G.	W.	3,620	129.8	15.0
E. H.	W.	3,550	124.4	25.6
B. H.	W.	3,800	150.5	28.6
A. I.	W.	2,360	149.9	32.6
E. J.	C.	3,040	151.8	34.4
D. J.	C.	3,000	85.0	14.9
M. J.	W.	3,850	295.4	36.0
R. K.	W.	3,310	129.8	62.5
S. M.	C.	3,180	61.6	21.3
E. R.	W.	3,920	85.8	20.0
E. S.	W.	2,670	123.8	22.4
M. S.	W.	3,110	144.0	34.4
C. S.	C.	2,760	117.0	28.4
B. T.	C.	2,675	46.2	14.2
M. T.	W.	3,700	189.0	33.7
A. W.	C.	2,675	99.8	33.8
P. W.	C.	3,775	79.2	20.5
R. W.	C.	3,010	164.3	26.6
E. W.	C.	2,470	124.4	27.7
G. Z.	W.	3,400	97.4	13.8
Average		3,201.2	131.4	28.6

*From *Shettles, Delfs and Hellman:* Bull. Johns Hopkins Hosp. 65: 419, 1939.
†Double ovum twins.

Since observations on a substantial series of cases had shown that the plasma prothrombin level of the newborn can be raised at will by the

TABLE II.* THE PLASMA PROTHROMBIN LEVELS OF MOTHER AND CHILD, EXPRESSED IN DILUTION UNITS, IN TEN FULL-TERM DELIVERIES FOLLOWING TREATMENT OF THE MOTHER DURING LABOR

NAME	INFANT WEIGHT	HOURS FROM ONSET OF TREATMENT TO DELIVERY		PROTHROMBIN DILUTION UNITS		
				MOTHER PRIOR TO TREATMENT	MOTHER AT DELIVERY	INFANT AT DELIVERY
		hr.	*min.*			
V. P.	3,550	19	59		231.9	148.5
M. Y.	3,310	16	57		272.8	81.2
M. Z.	3,410	14	50		273.7	78.0
E. O.	3,260	12	38	221.0	261.8	72.0
E. M.	3,040	11	43	136.3	162.3	66.6
E. J.	3,080	6	57	173.7	238.3	71.5
R. B.	3,075	6	39	128.7	175.6	70.5
M. B.	3,750	4		253.4	296.0	67.7
L. S.	3,220	1	40	155.8	191.4	53.9
D. C.†	2,875	1	29		116.0	21.6
Average	3,347.8			178.1	233.7	78.7

Dose of vitamin K concentrate, 9,000 units.
*From *Shettles, Delfs and Hellman:* Bull. Johns Hopkins Hosp. 65: 419, 1939.
†Not included in the average. Duration of treatment too short to be effective.

antenatal administration of vitamin K to the mother, the question at once arose as to the practical value of such a procedure. Would it diminish neonatal mortality by eliminating a certain group of hemorrhagic conditions? It was realized, of course, that massive cerebral hemorrhage resulting from severe birth trauma could not be prevented by this measure. However, it is common experience that many infants succumb to cerebral hemorrhage several days after delivery; thus, in Craig's careful pathologic study of 126 neonatal deaths from cerebral hemorrhage,[8] it was found that the majority of the deaths occurred between the second and sixth day, and some as late as the second and third week. The evidence suggests that in these cases minimal trauma at birth precipitated small hemorrhages which continued to ooze over a number of days; and it would seem conceivable that some of these infants might have been saved had their blood at birth exhibited better clotting properties. So far as outright hemorrhagic disease is concerned (estimated as occurring once in 200 cases), here we would expect the antenatal administration of vitamin K to offer positive prophylaxis.

But these considerations are theoretical only, and in order to test their validity, the following program of study has been carried out. Beginning Sept. 1, 1939, every other patient in labor admitted to the Obstetrical Service of the Johns Hopkins Hospital was given vitamin K by mouth. The preparation used was 2-methyl-1, 4 naphthoquinone, in a single dose of 2 mg.; this synthetic product is known to possess four times the potency of the vitamin K concentrate (vitamin K_1) used by Hellman and Shettles in their prothrombin studies reported in Tables I and II. Preliminary observations, moreover, showed that when this substance is fed to mothers during labor, a smaller dose is necessary to raise the plasma prothrombin of the infant and its action is more rapid. As of May 1, 1940, 384 mothers had received vitamin K in labor, while the alternate control series numbered 392. The two series were similar

in every respect, the distribution of patients according to race, parity, contracted pelvis, operative incidence, and premature labors, being approximately the same in the two groups.

It would seem pertinent to inquire first whether any harm can accrue, either to mother or child, from the administration of vitamin K in labor. So far as could be determined, there were no ill effects in this series of 384 cases. The puerperal morbidity was the same in the two groups. Concerning puerperal thrombophlebitis, the incidence of which might conceivably be increased as a result of the raised plasma prothrombin of the mother, there were two cases in the control series and one in the vitamin K group. The question is often asked whether vitamin K affects post-partum hemorrhage. Since blood loss after delivery is controlled by contraction of the uterine muscle fibers and not primarily by blood coagulation, no specific effect would be anticipated; and this supposition was borne out in the present study, the incidence of post-partum hemorrhage and the degree of blood loss at lower levels being approximately the same in the two groups. There were two maternal deaths in the vitamin K series.

The first occurred in a 31-year-old, colored para vii, whose previous 6 infants had been delivered per vaginam without difficulty. She had a contracted pelvis, however, with a diagonal conjugate of 10.5 cm. In the present labor, brow presentation of an eight-pound baby resulted in spontaneous rupture of the uterus, after seventeen hours of labor. Death occurred eleven days after hysterectomy, from subphrenic abscess and pneumonia. The other maternal fatality in the vitamin K series occurred in a normal, twenty-two-year-old, colored primigravida, five minutes after the administration of caudal anesthesia; chemical studies showed that the novocaine had been injected into the spinal canal rather than into the caudal space. It would seem evident that these two deaths were in no way related to the fact that the mother had received vitamin K. In the control series there were no maternal deaths.

Turning now to the newborn, the neonatal course of surviving infants was similar in the two series, the weight at discharge in relation to the birth weight being the same in the two groups. The stillbirth and neonatal mortality figures are as follows: Control series, 16 deaths, or 4.1 per cent mortality; vitamin K series, 6 deaths, or 1.5 per cent mortality. The infant death rate in the control series, accordingly, was 2.7 times that in the vitamin K group. Statistical analysis of these figures shows that they are probably significant; indeed, the chances are 45.6 to 1 against the likelihood that the difference in death rates in the two series was due solely to sampling error.

From a clinical viewpoint, these findings become more significant when the autopsy studies on these infants are reviewed.

As may be seen in Table III, hemorrhage was demonstrable at autopsy in but one of the six fatal cases in the vitamin K group, No. 6; this baby weighed eight and three-fourths pounds, presented by the breech with a hand prolapsed, and died in the course of a difficult breech extraction; autopsy showed subarachnoid hemorrhage. In the control series, hemorrhage into one or another organ was demonstrable in 9 of the 16 autopsies, or in 56 per cent (Table IV). In one instance, Case 12, we were obviously dealing with an outright case of hemorrhagic disease, necropsy revealing extensive hemorrhages in the cerebral vault, lungs, spleen, adrenal, and intestines; plasma studies on this baby before death showed that the prothrombin concentration was too low to be read. In Cases 13, 14, and 15, extensive cerebral

hemorrhage was present, sufficient to account for the death of the baby. Although the hemorrhages in Case 16 were small in degree, their widespread character suggests that they may have been responsible for the death of the baby, in the ab-

TABLE III. INFANT DEATHS AMONG 384 CASES IN WHICH THE MOTHERS RECEIVED VITAMIN K DURING LABOR. UNLESS OTHERWISE STATED NO HEMORRHAGE WAS DEMONSTRABLE AT AUTOPSY

NO.	HIST. NO.	TYPE OF DELIVERY	WEIGHT (GM.)	AGE	AUTOPSY
1	179744	Spontaneous	1,150	7 Hours	Prematurity; atelectasis
2	199012	Low forceps	1,360	2 Days	Prematurity; atelectasis
3	192634	Spontaneous	2,025	Stillborn	Prematurity; atelectasis
4	187349	Spontaneous	2,860	8 Hours	Aspiration gastric contents
5	121085	Rupture of uterus	3,740	Stillborn	Lungs unexpanded
6	121354	Breech extraction	3,980	Stillborn	*Hemorrhage*, subarachnoid

TABLE IV. INFANT DEATHS AMONG THE 392 ALTERNATE, CONTROL CASES IN WHICH THE MOTHERS DID NOT RECEIVE VITAMIN K. UNLESS OTHERWISE STATED, NO HEMORRHAGE WAS PRESENT AT AUTOPSY

NO.	HIST. NO.	TYPE OF DELIVERY	WEIGHT	AGE	AUTOPSY
1	190818	Low forceps	1,145	10 Hours	Prematurity; atelectasis
2	136565	Spontaneous	1,320	2 Days	Pneumonia; *hemorrhage*, subcapsular of liver; cephalhematoma
3	187672	Spontaneous	1,390	18 Hours	Prematurity; atelectasis
4	125648	Cesarean section, placenta previa	1,350	19 Hours	Prematurity; hyaline membrane
5	125648	Cesarean section, placenta previa	1,180	6 Hours	Prematurity; atelectasis
6	102128	Cesarean section, pre-eclampsia	1,670	24 Hours	Prematurity; *hemorrhage* in lungs and thymus
7	121686	Spontaneous	2,375	Stillborn	Atresia of duodenum
8	129796	Spontaneous	1,965	8 Hours	Prematurity; atelectasis
9	190295	Cesarean section, repeat	2,780	2 Days	*Hemorrhage*, pulmonary
10	193499	Cesarean section, pre-eclampsia	2,000	4 Days	*Hemorrhage*, pulmonary
11	198014	Spontaneous	3,185	Stillborn	Atelectasis
12	181103	Breech extraction	3,435	3 Days	*Hemorrhagic disease*
13	185441	Breech extraction	2,970	18 Hours	*Hemorrhage*, cerebral
14	178584	Version and extraction	2,500	Stillborn	*Hemorrhage*, cerebral
15	173614	Low forceps	3,160	1 Hour	*Hemorrhage*, cerebral
16	177143	Spontaneous	3,985	2 Days	*Hemorrhages*, minute in brain, lungs, spleen, adrenal, thymus, and liver

sence of other pathologic changes; the clinical course of the case was at variance with the view that they were secondary to anoxia, although such a contention cannot be disproved. In regard to the three cases (Nos. 6, 9, and 10) in which pulmonary hemorrhage was encountered at autopsy, such findings have been subject to various interpretations; certain observers attribute them to a hemorrhagic diathesis which kills the infant before other organs are involved; others regard them as evidence of an overwhelming pneumonia, while some ascribe them to anoxia. Summarizing Table IV, in 4 of the 16 deaths, hemorrhage appeared to be the direct cause of death; it was present in 5 additional cases and doubtless played a certain role in the fatal outcome, but one which is difficult to evaluate with assurance. In view of the fact that autopsy revealed the presence of hemorrhage in 9 of the control cases and in but one of the vitamin K series, the findings are in keeping with the view that the antenatal administration of this vitamin eliminated a certain number of hemorrhages.

In order to investigate further the efficacy of antenatal administration of vitamin K in diminishing hemorrhage in the newborn, a series of observations was made on the retinas of infants in these two series. These studies were carried out by Dr. Alfred E. Maumenee, of the Department of Ophthalmology, who will presently report them in detail.

A preliminary survey shows the following figures: Among 92 infants in the control group, retinal hemorrhage was demonstrable in 29 cases, or in 32 per cent; among 75 infants in the vitamin K series, there were 12 retinal hemorrhages, an incidence of 16 per cent. The frequency of retinal hemorrhage in the control group, accordingly, was twice that in infants whose mothers had been treated prophylactically with vitamin K. Statistical analysis shows that these figures are significant, the chances being 82.5 to 1 against the likelihood that the difference in the two series is due to sampling error.

What, now, are we to conclude from these observations? Most fundamental is the fact that present-day plasma prothrombin studies have given us a new conception of hemorrhagic diathesis in the newborn. Far from being a disease entity unto itself, it represents simply an extreme degree of a condition, hypoprothrombinemia, which all newborn infants exhibit to a certain extent and in various gradations. Unless the plasma prothrombin level is extremely low, this hypoprothrombinemia may be without clinical manifestations. However, if birth trauma, anoxia, and other causes of bleeding are superimposed upon it, this prothrombin lack must necessarily play a part in the duration, and, therefore, in the extent of the bleeding. Along with trauma and anoxia, then, hypoprothrombinemia must be regarded as a factor in the outcome of every case of bleeding in the newborn, whether cerebral or otherwise; and it is the one factor in this triad, let us recall, which is subject to prophylactic correction. To what extent will the routine antenatal administration of vitamin K diminish hemorrhage in the newborn and thereby reduce neonatal mortality? We believe, in the first place, that such a practice, properly timed and with suitable dosage, will well-nigh eliminate so-called hemorrhagic disease of the newborn. In the second place, the facts indicate that certain types of cerebral hemorrhage, particularly small hemorrhages which ooze over a number of days, may be preventable by this procedure. To what slight extent the elimination of such deaths would diminish neonatal mortality, it is obviously impossible to state, but the evidence presented would seem of sufficient promise to warrant recommending the routine antenatal administration of vitamin K for trial.

REFERENCES

(1) *Jacobs, M. W.:* J. A. M. A. **83:** 1641, 1924. (2) *Edgerton, A. E.:* Arch. Ophth. **11:** 838, 1934. (3) *Sharpe, W., and Maclaire, A. S.:* Am. J. Obst. & Gynec. **9:** 452, 1925. (4) *Brinkhous, K. M., Smith, H. P., and Warner, E. D.:* Am. J. M. Sc. **193:** 475, 1937. (5) *Moore, R. A., and Javert, C. T.:* Personal communication. (6) *Hellman, L. M., and Shettles, L. B.:* Bull. Johns Hopkins Hosp. **65:** 138, 1939. (7) *Shettles, L. B., Delfs, E., and Hellman, L. M.:* Bull. Johns Hopkins Hosp. **65:** 419, 1939. (8) *Craig, W. S.:* Arch. Dis. Childhood **13:** 89, 1938.

DISCUSSION

DR. WILLIAM C. MENGERT, Iowa City, Iowa (by invitation).—Hemorrhagic disease of the newborn is now a well-understood entity with a sound therapeutic basis in vitamin K administration. Transfusion of blood, previously the best available treatment, represented a replacement of plasma prothrombin, often raising the level above that necessary to protect from hemorrhage. Even now, however, blood transfusion cannot be lightly discarded, since following massive hemorrhage it remains a valuable procedure, whether or not vitamin K has been administered.

Although it appears that etiologic and therapeutic considerations in hemorrhagic disease of the newborn are well understood, such is not true with a certain group of cerebral hemorrhages which generally cause death between two and six days after birth. Presumably, injury or anoxia in association with poor clotting power of the blood are concerned in etiology. It is well known that in addition to a low plasma prothrombin level at birth the newborn child suffers further depression of this level between the second and sixth days. The exact part each of these two factors, initial injury and low plasma prothrombin level, plays in etiology is not clear.

Dr. Eastman has now shown that antenatal administration of vitamin K to the mother causes a significant decrease in the number of cerebral hemorrhages both fatal to and contributory to the death of the newborn, and in the number of retinal hemorrhages. His work has been so well controlled that one tends to agree with the suggestion that routine antenatal administration of vitamin K to the mother be given an adequate trial.

Since the plasma prothrombin level is an index of vitamin K activity, it would be interesting to know what were the levels in the babies of this series, especially those who died. With such data, considerable light might be thrown on the relative parts played by trauma, anoxia, and low plasma prothrombin in the production of cerebral bleeding. From a practical standpoint we should know if it is desirable to secure adult or nearly adult levels of plasma prothrombin in the newborn. On the other hand, may it not be sufficient merely to prevent the depression of the level which occurs between the second and sixth days?

Until extensive data on plasma prothrombin levels, correlated with clinical observations, are available so that those babies who need additional vitamin K can be readily recognized, it seems reasonable to administer it directly to all babies or indirectly to the mother before the onset of labor. In view of the greater fetal gain from treatment of the mother compared with direct administration to the newborn infant, as shown by Eastman and his associates, perhaps it is better to employ the former method, at least for the time being. Apparently no observer has yet reported harm to either mother or baby from therapeutic doses of vitamin K administered to either. Certainly, the cost of the drug is not a barrier to its routine use.

Certain problems concerned with bleeding in the newborn may well be elucidated by future work. For example, in view of the comparatively rich content of vitamin K possessed by leafy vegetables and grasses, and their general availability during the summer and early fall, one should look for a seasonal fluctuation in the number of cerebral and retinal hemorrhages in the newborn.

Although routine administration of vitamin K will prevent hypoprothrombinemia in the newborn and thus inhibit a certain amount of slow bleeding, it cannot prevent the basic injury which originated the bleeding. Granting that in many instances this basic injury may be insignificant, nevertheless follow-up studies to ascertain the ultimate outcome of these babies will surely be desirable.

DR. ALFRED C. BECK, Brooklyn, N. Y.—Several years ago observations in our Clinic seemed to indicate that the incidence of intracranial hemorrhage and hemorrhagic disease in the newborn were increasing. Because a large percentage of our patients were on relief and accordingly might well have had deficient diets, the possibility of a dietary deficiency as the cause of this increased hemorrhagic tendency was considered. Soon after the early work on vitamin K appeared, we therefore undertook a study somewhat similar to that which Dr. Eastman has reported. Every third service patient, accordingly, was given 2 mg. of the synthetic vitamin K by mouth one hour or longer before the birth of her child. Another third of our patients received oxalic acid, as suggested by Dr. Schumann before this Society. The remaining third was used as controls, the three series being carried on concurrently.

Vitamin K was given to 504 women, and 612 concurrent patients were observed as controls. In the vitamin K series, 4 newborn infants had intracranial hemorrhage and 2 additional ones had bloody stools, making a total of 6, or 1.2 per cent, which might have had a hemorrhagic tendency. In the control series, 11 newborn infants had intracranial hemorrhage and bloody stools were observed in an additional 9. In contrast with the K series, therefore, 20, or 3.2 per cent, of the control babies had hemorrhagic tendency. In other words, bleeding occurred almost three times as often in the babies whose mothers did not receive vitamin K as a prophylaxis.

This slide* is a graphic representation of the effect of the prophylactic administration of vitamin K on the prothrombin activity of a newborn infant. The figures on the base line represent the prothrombin activity as a percentage of that which is observed in the normal adult. The perpendicular figures indicate the number of cases. Your attention is called, first, to the three control graphs in the lower half of the slide. These represent the results of 300 prothrombin determinations made in 100 cases on the first, second and fourth days after birth. In order that you may understand the graph more clearly, this block represents eight cases whose prothrombin activity was from 30 to 40 per cent of the normal. This block represents 31 cases whose prothrombin activity was 70 to 80 per cent of the normal. The perpendicular line is the mean of the entire polygon. As you may observe, the mean of the hundred controls on the first day was 72.6 per cent. This mean fell to 59 per cent on the second day and returned to 72.3 per cent on the fourth.

The upper half of the slide shows the results of analogous observations made on another hundred infants born to mothers who had had the prophylactic administration of vitamin K. In this group, the mean prothrombin activity was 92.9 per cent of the normal on the first day, 90 per cent on the second, and 91 per cent on the fourth. In other words, the prophylactic use of vitamin K seemed to prevent the diminished prothrombin activity which normally is observed on the second day of life. By preventing this fall in the prothrombin level, the tendency to hemorrhagic disease must be diminished, as was shown by Dr. Eastman in his clinical observations and as has been corroborated by our observations in a somewhat larger number of cases. In addition, this slide shows a very pronounced shift to the right in the vitamin K cases. On the first day, as well as on the critical second day after delivery, the number of infants with a low prothrombin activity was much smaller in the vitamin K series than in the controls.

DR. GEORGE W. KOSMAK, New York, N. Y.—I would like Dr. Eastman to tell us whether any patient of this series received barbiturate analgesics?

DR. WILLIAM E. CALDWELL, New York, N. Y.—I would like to know about Dr. Beck's results with the use of oxalic acid in order to follow up the discussion of last year.

DR. E. L. KING, New Orleans, La.—I would like to ask about three points: (1) The determination of the prothrombin level; (2) the time to begin the administration of vitamin K to the mother before delivery; and (3) the advisability of giving vitamin K to infants, delivered by mothers who have not had vitamin K, before circumcision, especially if the coagulation time is slow.

*This slide will appear in a paper to be published in a later issue of the JOURNAL.

In the Charity Hospital in New Orleans we have 350 or more deliveries a month, all in the very low level economic group. We happen, however, to be in a region where because of our climate practically all patients can obtain proper diet at any time of the year. Would it be, in Dr. Eastman's opinion, worth while to give these patients prophylactic vitamin K in spite of that? The economic phase of the question comes up there because of the additional expense.

DR. BECK.—In answer to Dr. Caldwell's question but on the basis of incomplete studies I might say that thus far we have noticed that there is some diminution in the hemorrhages with the use of oxalic acid, although it is not as great as with vitamin K.

DR. FRED L. ADAIR, Chicago, Ill.—I would like to ask whether some of these effects are not due really to a deficiency diet in the patient, and whether it may not be unnecessary to extend this treatment to all people in all economic strata.

In both series were all babies alive when the vitamin K was administered to the mothers?

DR. LOUIS M. HELLMAN, Baltimore, Md. (by invitation).—Dr. Eastman asked me if I would answer some of the questions.

In response to Dr. Mengert, I am sorry to say that, inasmuch as the method used for the analysis of prothrombin requires 3 to 4 c.c. of blood, we have not been able to obtain levels on all the infants that died. Those that we did determine were all low.

As to the question of seasonal variation, Dr. Waddell of the University of Virginia has noted a seasonal variation in the prothrombin of both mothers and infants. We have found the same to be true. This obviously should be so, especially in Baltimore, where a large percentage of the negro population lives on a marginal diet consisting largely of vegetables in the summer and canned goods in the winter.

Dr. Beck's slide showed a hemorrhagic tendency in some of the infants born of treated mothers. This has been our experience too, and is well demonstrated by the studies on retinal hemorrhage. In our clinic this type of hemorrhage occurs in about 32 per cent of newborn infants. The hemorrhage is of the oozing variety and not due to capillary rupture. It should therefore be prevented by raising the prothrombin level; and in the series of infants of treated mothers, the incidence of retinal hemorrhage was reduced to 15 per cent. These infants did not have elevated prothrombins, in spite of the fact that the mothers had received vitamin K. On the other hand, in a small series of 15 deliveries where the mothers had received 2 to 4 mg. of vitamin K daily for four or five days prior to delivery, there were no retinal hemorrhages and the prothrombin levels of the infants were very high in each instance. And thus, in response to Dr. King's question, while the results are good when therapy is given during labor, it would seem that the optimum time of administration should be the last week of gestation.

For the determination of prothrombin, we have used the method of Smith, Warner and Brinkhous, described in 1934. Roughly this method consists of the removal of all substances in the plasma related to clotting except the prothrombin. An artificial clot is then made by adding standardized reagents to various dilutions of this prothrombin. The dilution necessary to form a clot in fifteen seconds determines the dilution unit. While this procedure is very accurate, it requires a skilled technician. The quick method is much simpler and yields essentially similar results. It is certainly much more applicable to clinical work.

Dr. Kosmak asked about the administration of barbiturates in the two series reported. About one-third of our ward patients receive some sort of analgesia. The incidence was the same in both groups.

When vitamin K is administered directly to the newborn infant, we have used 1,000 units or ½ mg. a day for four days. This can be divided between the feedings. However, the prothrombin level of infants can be elevated to a greater degree by administering the vitamin to the mothers prior to delivery. This may be merely a matter of absorption, and perhaps some of the parenteral substances,

available now only for experimental purposes, should find a field in infant administration. The question seems to be the advisability of attempting to control cerebral hemorrhage which may have already done considerable damage. We have had two rather unfortunate instances where babies with cerebral hemorrhage have received vitamin K. In both cases the babies lived, but they will never develop normally. I think that it is far better to treat the babies yet unborn, through the mother and thus protect them during labor.

Replying to Dr. Adair's question as to whether the babies in these two series were all alive on admission, the answer is that we eliminated all cases where the fetal heart could not be heard on admission to the delivery floor.

Also in reply to Dr. Adair, it has been very well shown by many workers that all newborn infants have a low prothrombin. It would certainly be practical to treat all mothers in labor, even if it were only to prevent hemorrhagic disease. As a matter of fact, the only deaths on our service from hemorrhagic disease, since the use of vitamin K, with the exception of the case mentioned by Dr. Eastman, have occurred on the private service where vitamin K is not routinely used.

DR. EASTMAN (closing).—I should like to make it clear that the major part of this work on vitamin K was done by Dr. Louis M. Hellman and Dr. Landrum B. Shettles, of our Department of Obstetrics, whose names will appear as co-authors of the paper.

THE MANAGEMENT OF THE ADHERENT PLACENTA IN THE PRESENCE OF INFECTION*

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(From the Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry)

THE abnormally adherent placenta may at times constitute a very serious problem. Opinions still differ in regard to the length of time one should wait for separation to occur before resorting to manual removal of the organ, provided there is no associated active bleeding; but, in general, nearly all authorities now feel that at least one to two hours should elapse before a manual removal is resorted to unless active bleeding should necessitate its earlier performance. The reason for delay before resorting to manual removal is, of course, to be found in the dangers attending this procedure and in particular the possible resulting infection. The mortality attending this procedure has in the past been placed at around 10 per cent, which would obviously place the procedure in the definitely hazardous class of obstetric operations. To avoid these associated dangers, some have even suggested that in the absence of bleeding, much longer periods of time than the usually accepted one or two hours should elapse before resorting to manual removal. In 1915 the late John O. Polak rather startled the members of this Society by presenting a case in which the placenta was allowed to remain in situ for four days before it was finally removed by expression, and in the absence of bleeding, he recommended waiting indefinitely, days if necessary, before resorting to manual removal.

On the other hand, a number of Scandinavian and French authors have recently presented fairly large series of manual removals with a much lower mortality than has hitherto been recorded. Thus Schie, in Oslo, found in 189 such procedures the mortality included only three patients, or 1.58 per cent. In each of these three instances, death was due to puerperal infection, and it is interesting to note that in two of these women, the manual removal was apparently performed in the presence of an already existing infection.

Personally, I still regard the procedure as a dangerous one, though I accept the usual indications of hemorrhage or delay in separation beyond two hours with no bleeding as sufficient reason for carrying out manual removal. As already pointed out, the particular menace attending manual removal of the placenta is to be found in infection. Undue prolongation of the third stage of labor to many hours or even days, may as in Polak's experience, be at times quite innocuous, but on the other hand, it may also result in the very situation that we are trying to avoid, namely the invasion of the uterus by pathogenic organisms.

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

When infection is already established in the presence of an adherent placenta, the problem becomes still more formidable. In reviewing the literature on the subject, I was surprised to learn how little attention has been paid to this angle of the problem. In current textbooks, Adair alone makes mention of the added menace, but Eastman also draws attention to it in his recent review of the literature on obstetric hemorrhage.

I propose to present two examples of this complication which occurred on my service with an outline of the procedures followed.

CASE 1.—L. M. (Unit No. 115282), aged 23 years, para iii, all previous labors normal. In this, her fourth pregnancy, she was delivered spontaneously in her home by her physician, two days before admission to the hospital. Numerous efforts at the Credé maneuver were unsuccessful, and there was no associated bleeding. After forty-eight hours, she was given gas oxygen anesthesia, and an attempt was made to remove the placenta manually. This was unsuccessful but did cause considerable bleeding so she was then sent to the hospital May 22, 1936. On admission she appeared to be gravely ill; temperature, 39.3° C.; pulse, 170; blood pressure, 85/50. She presented a waxy white appearance and was obviously suffering from the effects of hemorrhage and infection, though bleeding at the time of admission was slight. Red blood count was 2,690,000; hemoglobin, 6.2 Gm.; white blood count, 18,100. In view of the history, some consideration was given to the possibility of placenta accreta, but she was obviously in no condition for a major operation, so efforts were directed toward improving her general condition by transfusion and the other usual general measures. Six hours after admission and fifty-four hours after delivery, she spontaneously expelled the bulk of the placenta, but there was an obvious defect in it, representing an absence of tissue from an area of about 8 by 4 cm. The expulsion of tissue was accompanied by the loss of approximately 150 c.c. of blood and no further bleeding occurred. Her general condition had improved somewhat at this time, but was still precarious, so it seemed unwise to adopt any immediate measures for the recovery of the retained fragment of placenta. Twelve hours later this remaining fragment was expelled spontaneously with no associated bleeding. Her convalescence was stormy, with evidence of serious infection persisting for four weeks, and she developed a mild thrombophlebitis of the left leg during the puerperium. Blood cultures were persistently negative. She eventually recovered and was discharged from the hospital six weeks after admission.

Microscopic examination of the placenta showed no unusual invasion of the covering decidua by the chorionic villi. An acute placentitis was present with fairly extensive leucocytic infiltration throughout.

She was seen again last year, when she aborted spontaneously at six months with no attendant complications.

CASE 2.—L. G. (Unit No. 121075), aged 32 years, para i, had had one miscarriage. Her first pregnancy was terminated in another city by induction of labor at term, apparently on account of a toxemia. The child died immediately after birth, and the patient sustained a third degree tear which was later repaired. Her second pregnancy terminated in early spontaneous abortion. In her third pregnancy she was first seen by me on July 19, 1938, when she was about two months pregnant, the calculated date of confinement being Feb. 23, 1939.

This pregnancy proceeded quite uneventfully until Dec. 18, 1938, when the membranes suddenly ruptured. She was promptly admitted to the hospital. On admission she was not in labor, but the membranes were obviously ruptured. The uterus was the size of a seven months' pregnancy, and the fetal heart sounds were normal. She presented evidence of a slight upper respiratory infection, but apart from this her general condition was satisfactory. There were no further developments for seven days, when she began to have irregular painful uterine contractions. Coincident with the onset of labor she had a chill and a temperature elevation to 39.5° C. Labor progressed very slowly, apparently on account of irregular and inefficient uterine contractions, but after thirty hours she was delivered spontaneously

of a premature living child, weighing 1,880 Gm. The amniotic fluid escaping after the birth was greenish in color, and had an offensive odor. Cultures taken at the time later showed a mixed growth of organisms with *Strep. viridans* and nonhemolytic streptococci predominating. The blood cultures were negative. After delivery of the child there was no bleeding and the placenta failed to separate. After one-half hour the Credé maneuver was resorted to without success, and several succeeding attempts also failed. She was given a sedative and allowed to rest, but was kept under constant supervision. Under ordinary circumstances manual removal would have been resorted to, but in the presence of the obvious infection this seemed contraindicated. Twenty-four hours later there was no change in the uterus and no bleeding. The temperature fell to normal, but later in the day another chill occurred with a temperature elevation to 40° C., and the patient appeared quite ill. Other attempts at Credé's expression were unsuccessful. Forty-eight hours after delivery she expelled a small clot, the first bleeding that had occurred, but again efforts at expression failed. The temperature continued elevated but was tending to decline. On December 30, ninety hours after delivery, she expelled the intact placenta spontaneously along with approximately 200 c.c. of blood. Her further convalescence was uneventful, the temperature subsiding immediately and remaining at a normal level for the remainder of her hospital stay. During her febrile period before separation of the placenta, two small transfusions were given.

Microscopic study of the placenta revealed extensive inflammatory reaction in the subamniotic connective tissue, and a section stained for bacteria showed numerous short gram-positive chains and diplococci in this same region. Little inflammatory reaction was discovered in the body of the placenta and none at all in the decidua. The decidual layer was quite thin, but there was no evidence of undue penetration of it by proliferating chorionic villi.

In this patient, the source of the infection is undoubtedly to be found in the premature rupture of the membranes with the long interval elapsing between that occurrence and the onset of labor with the resulting invasion of the sac of the ovum by pathogenic organisms. Such intrapartum infection is also a menace to the child from the possible so-called "placental bacteriemia," as emphasized by Slemons. It is of interest to note in this connection that a culture of the cord blood showed the presence of colon bacilli. The baby, however, did extremely well and was discharged from the hospital after five weeks, weighing 2,950 Gm.

COMMENT

In these two patients the end result was quite satisfactory following a conservative line of treatment, and the result would appear to justify the treatment followed. The problem of the adherent placenta and associated infection may well be compared to the infected incomplete abortion. In this latter condition we have had many serious experiences in the past as the result of interference during the period of active infection, and unfortunately many years elapsed before the profession came to an appreciation of the risks involved and abandoned interference except in the presence of active bleeding. At present if there be no associated hemorrhage, we never think of removing the retained placental tissue in the incomplete abortion until several days after the evidence of infection has subsided, and the results following such conservative therapy are far superior to those obtained during the period when active intervention was the rule. It would seem reasonable to apply similar rules to the situation under consideration, that is, wait until the infection has subsided and then resort to manual removal. At the same time we must admit that the menace in the case of the adherent full-term placenta with associated infection is greater than would be the case in the earlier abortion. The risk is greater because, if a

partial separation should occur during the waiting period, the hemorrhage might well be much greater than would be the case in the earlier pregnancy. For this reason, and because it might occur quite suddenly, the patient should never be left unattended while the placenta is still in utero, and preparations to facilitate immediate interference should be kept constantly available.

In this situation, if partial separation with hemorrhage should occur, one's hand is forced. If the emergency is serious, it may be necessary to disregard the menace of infection and remove the placenta manually at once to prevent further hemorrhage, or on occasion it might seem preferable to control the bleeding temporarily by packing the uterus, and then resort to abdominal hysterectomy. Either will be hazardous, and the choice of procedure will depend on the circumstances present at the time the emergency arises.

In considering factors possibly responsible for prolongation of the third stage of labor, three main possibilities must be considered, and it is important to make proper differentiation between them. Thus, the placenta may separate and yet be retained in utero by the contraction ring; it may be abnormally adherent; or more rarely, we may be dealing with a true placenta accreta. Differentiation between the first two of these conditions is usually not difficult. Recognition of a placenta accreta, however, can only be by manual exploration of the uterine cavity, and the diagnosis is usually established on discovering the impossibility of removing the placenta manually. In both of our patients, consideration was given to the possibility of a placenta accreta being present, but in the first patient her condition was too critical at the time of admission to permit exploration of the uterus; while in the second, we felt that the infection present contraindicated exploration. In our second case then, the diagnosis was held in abeyance until the problem solved itself by spontaneous separation and expulsion of the placenta.

In these two patients, we were quite confident from the evidence at hand that we were dealing with abnormally adherent placentas and not simply with retained placentas; but in the second case, in particular, an additional late observation gave convincing evidence that this was the situation. This later observation was made in connection with the establishment of lactation, which did not occur until the third day after the placenta had been expelled or the seventh day after the birth of the child.

Such an observation appears to support the current theory that the onset of lactation may be due to a deprivation of certain hormonal substances originating in the placenta, possibly estrin or progesterone, or both, and that lactation is held in abeyance while these are being actively produced, which would be the case while the placenta is in active organic union with the maternal organism.

SUMMARY AND CONCLUSIONS

Two examples of abnormally adherent placenta and associated infection are presented. Both were treated conservatively but both made good recoveries.

Manual removal of the placenta is the usual method of procedure for such a condition, and generally speaking, this may be resorted to if after two hours, in the absence of bleeding, the simpler methods have failed to bring about separation and expulsion of the organ. Undue prolongation of the third stage may well result in the very accident we are trying to avoid, namely, partial separation with hemorrhage or invasion of the uterus by pathogenic organisms. Should bleeding occur, resort to this procedure may be necessitated earlier.

In the presence of associated infection however, manual removal of the placenta becomes a truly hazardous procedure and should not be employed during the period the infection is active unless active bleeding supervenes and necessitates interference. Occasionally supravaginal hysterectomy may be the preferable procedure. Attention is drawn to the delay in the onset of lactation while the placenta remains attached to the uterine wall.

REFERENCES

Adair: Textbook of Obstetrics and Gynecology, 1940. *Eastman, N.:* Obstetric Hemorrhage, New International Clinics 3: Series 2. *Polak, John O.:* Trans. Am. Gynec. Soc., 1915. *Schie, E.:* Acta obst. et gynec. Scandinav. **19**: 28, 1939. *Slemons, J. Morris:* J. A. M. A. **65**: Oct. 9, 1915.

DISCUSSION

DR. GEORGE KAMPERMAN, DETROIT, MICH.—We have for a long time accepted the principle that puerperal patients with fever should be treated very conservatively. An exception to this policy has been found only in certain cases where bleeding was of such proportion as to constitute a hazard.

On looking over the records of patients at Harper Hospital who had retained placental tissue with fever and excessive bleeding, we were rather surprised by the almost uniformly good results obtained by the removal of the retained placental tissue. In the last four years we have records of seven such patients treated actively, and all made rapid recoveries without complications or spread of infection.

We have, therefore, gradually developed a wider indication for interference in patients with the known retention of placental tissue. We are inclined to believe that the known retention of placental tissue in a patient with fever speaks for the diagnosis of sapremia rather than sepsis.

With this process of reasoning in mind I would like to report two patients about whom we were consulted during the past year. Both were delivered in their homes by their family doctors, and the failure of expulsion of the placenta called for consultation and later hospitalization. Both patients had had high fever for several days and seemed very septic and very ill. In both the Credé technique of placental expression had been repeatedly unsuccessful. Both patients were very anemic, although bleeding had not been a prominent symptom. One patient showed a positive blood culture, while in the other no blood culture was obtained. In both cases the placenta was removed by digital separation and extraction with a placental forcep. In one case the placenta was removed seventy-five hours after delivery, the temperature being 104.8° F. before delivery. Temperature dropped to almost normal within two days with an occasional rise for six days after that. In the second case the placenta was retained for nine days post partum, the fever rising to over 104° F. for several days before the removal of the placenta. Two days after the removal the temperature was normal and remained normal.

It would seem to us that the emptying of the uterus in such cases would favor involution and contraction and would tend to close the sinuses and lymphatics, and thus lessen the spread of infection.

To avoid these serious and trying situations it would seem there is no time so favorable for the removal of an adherent placenta as when the patient is clean and fresh. Theoretically, there is danger in invading the uterine cavity; yet with

proper technique and asepsis this is a fairly safe procedure. During the past three years we note 19 cases of manual removal of the placenta in the delivery rooms at Harper Hospital, and a careful study of the records shows no shock and no fever resulting in these 19 cases.

We believe a frank puerperal sepsis and puerperal fever due to an adherent or retained placenta are two different conditions. From the experience we have had with active interference where we thought it was indicated because of bleeding, we believe that the known retention of placenta, as well as the bleeding, should be considered an indication for active treatment.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—On the Obstetric Service of the Bryn Mawr Hospital during the past three years, there were 6 patients with retained placentas for more than twelve hours after delivery. All were primigravidas from 21 to 39 years of age. Four of the patients had sodium amytal or rectal ether analgesia, and two patients had no anesthesia at all. Two were delivered by low forceps, two delivered spontaneously, and in two rotation of a posterior occiput was practiced.

Our attitude toward a retained placenta after delivery has been the same as toward secundines which are not expelled after a miscarriage. The patients are placed in semi-Fowler position, given sedatives, ergot, and blood transfusions if these are indicated. Intrauterine packing is resorted to if the bleeding is profuse.

All of these patients had some fever. In three cases the temperature was over 104° F. and was accompanied by chills. In several instances where attempts at manual removal of the placenta were made, such efforts were invariably followed by an exacerbation of symptoms. All of our patients recovered, passing the placenta spontaneously; one on the second day, two on the fourth day, one on the fifth day, and two on the sixteenth day. We are convinced that patients with retained placentas should be treated conservatively.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—I would like to disagree with the idea that the placenta in utero has any restraining influence on lactation. Dr. Peter Freuchen who wrote that very interesting book, *The Frozen North,* reports many cases of Lapland women who, while nursing one baby, will become pregnant with another, nurse that one and again become pregnant at the same time, repeating this all their lives. If there were any evidence of the placenta influencing lactation it would be shown in these women.

There is a difference between a retained placenta and an adherent placenta, and a placenta increta. We know that the whole placenta may be safely left in the clean uterus, in the absence of hemorrhage, for several days. Ramsbotham even reports a case where the placenta did not come away at all, and he believed it had been absorbed, as it may be in ectopic pregnancy. On the other hand large pieces of the placenta may come away more or less broken up, in the lochia. An adherent placenta may require some time to separate, but usually bleeding demands treatment. Placenta increta is a different matter, for in these cases the placenta has grown into the muscle.

Dr. Wilson has proved that the post-partum uterus will handle more infection than we give it credit for. In septic abortion I have packed the cervix and vagina to stop bleeding, given blood to replace the previous loss, and thus tided the patient along until her immunities have been developed or until it was safe to invade the inflamed uterus. I wonder if such a policy would succeed with a full-term pregnancy. Would sulfanilamide be useful in such cases?

DR. E. L. KING, NEW ORLEANS, LA.—We have at times injected the placenta with about 200 c.c. of normal saline through the umbilical vein, and this has seemed to help in the separation of these retained placentas (Gabaston-Mombojou method).

DR. WILSON (closing).—Since one accepts the principle that one should not invade a uterus known to be infected, I continue to wait for separation in the absence of bleeding. On the other hand, if bleeding occurs, one's hand is obviously forced. If that should occur, one has the choice of two procedures, either to remove the placenta or to perform a hysterectomy.

We did not administer sulfanilamide because we did not know until later what organism had caused the infection.

A COMPARISON OF TWO CESAREAN SECTION SURVEYS CARRIED ON IN THE CITY OF NEW ORLEANS*

EDWARD L. KING, M.D., NEW ORLEANS, LA.

IN 1927 the New Orleans Gynecological and Obstetrical Society[1] reported the findings of a survey of the 300 cesarean sections performed in the city during the six years 1921 to 1926, inclusive, discussing the indications, techniques, results, etc. In 1938[2] the Society presented a review of the 1,108 sections performed in New Orleans during the ten years from 1927 to 1936, inclusive. We felt that this second survey would be of interest as a method of ascertaining whether the lessons learned from the first study had been taken to heart by the local profession. A review of these two investigations is presented to this Society, as I believe that the improvement in results demonstrates the value of a frank presentation of such data. I also feel that the Society would be interested in a consideration of the changes in thought and practice in this matter of cesarean section as shown by these two sets of figures.

TABLE I. 1921-1926

Total deliveries in city	61,966
Total deliveries in hospitals	16,323
Total cesarean sections	300
Cesarean percentage of total deliveries	0.48
Cesarean percentage of hospital deliveries	1.8
Cesarean, total deliveries ratio	1 to 206

Table I shows that in the first period of six years there were 16,323 hospital deliveries with 300 cesarean sections, an incidence of 1.8 per cent. The total deliveries in the city during this period were 61,966; cesarean section accounted for 0.485 per cent of these. In other words, in these six years one out of every 206 babies was delivered by the abdominal route. In Table II, covering the succeeding

TABLE II. 1927-1936

Total deliveries in city	92,936
Total deliveries in hospitals	52,629
Total cesarean sections	1,108
Cesarean percentage of total deliveries	1.19
Cesarean percentage of hospital deliveries	2.08
Cesarean section, total delivery ratio	1 to 84

ten years, we see that there were 52,629 hospital deliveries, with 1,108 sections, or 2.08 per cent of the total. There were 92,936 births in the city during this period; of these, 1.19 per cent were delivered by cesarean section. Thus, in this second group, one out of every 84 babies reached the world by laparotomy. In the first survey, it was found that approximately one-fourth of the total deliveries were in hospitals; in the second study, this ratio had increased to a little over one-half; and in the last three years of this time, two-thirds of the obstetric patients

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in the city were hospitalized. The percentage of sections in the hospital patients shows a slight rise, but the increase in the proportion of obstetric patients delivered in hospitals was associated with a rise in the percentage of sections to total births to a figure two and one-half times that in the first survey.

TABLE III. PERCENTAGE OF CESAREAN SECTIONS IN VARIOUS HOSPITALS

	FIRST SERIES	SECOND SERIES
New Orleans Charity Hospital	1.2	1.4
Hospital A	1.5	2.3
Hospital B	2.9	1.1
Hospital C	2.7	4.9
Hospital D	2.8	3.0
Hospital E	0.25	0.6

Table III shows the incidence of section in those hospitals from which complete data were obtainable for both periods. It will be noticed that the figures for the Charity Hospital are essentially the same, while there is an increased ratio in most of the private hospitals. In the case of Hospital B, the committee was informed that there were other sections in the second period, the records of which were not secured for study. Complete data might not have shown the reduction noted in the table. It is interesting to observe, incidentally, that in the first period 11.5 per cent of the total deliveries in the city were in the Charity Hospital, and that in the second this percentage rose to 31, the increase being particularly noticeable in the last three years, when the figure rose to 42 per cent.

TABLE IV. INDICATIONS

	FIRST	SECOND
Contracted pelvis	107	480
"Disproportion"	16	71
Cervical and vaginal lesions, benign	10	38
Carcinoma of cervix	1	3
Eclampsia	41	27
Other toxemias	12	51
Placenta previa	33	114
Premature separation of placenta	6	34
Cardiac lesions	4	22
Fibroids of uterus	2	15
Previous cesarean section (with 4 ruptured scars in first and 2 in second)	28	70
Inertia with prolonged labor	28	16
Prolapsed cord	2	0
Miscellaneous	10	167
	300	1108

Table IV presents a comparison of the indications for the operation in the two series. The records were much more specific in this regard in the second period. It will be seen that contracted pelvis accounted for about one-third of the operations in the first series and almost one-half in the second. The rather indefinite designation "disproportion" was noted in about the same proportion in both. The drop in the figures for eclampsia (from 14 per cent to 2.4 per cent) is most striking. We were surprised to find that there had been no increase in the proportion of sections for placenta previa, the percentages being 11 and 10.3, respectively. The committee was under the impression that there had been quite an extension of this indication, and we find that this is true for the past few years. The figures for previous section seem low, but this is accounted for by the fact that many repeat operations were listed under the original heading of contracted pelvis. There were really 50 "repeat" sections in the first series and 148 in the second. The low figures for uterine fibroids and prolapse of the cord are also worth noting.

"Inertia with prolonged labor," a rather unsatisfactory reason for the performance of the operation, dropped from 9 to 1.4 per cent. The miscellaneous group covers such conditions as elderly primiparity, malpresentation, previous myomectomy, contraction ring, etc.

TABLE V. TECHNIQUE

	FIRST SERIES	SECOND SERIES
Classical	175	545
Low segment	31	488
Porro	10	39
Portes	0	2
No details as to technique	84	34
	300	1108

Table V presents a tabulation of the techniques employed. The committee felt that the majority of the 84 operations in the first series which were not described in the records were of the classical type, and that thus the proportion was much greater than the 58.3 per cent shown. In the second series, the classical operation had dropped to 49 per cent, with the possibility that some of the 35 which were not described were in this group. The increase in the popularity of the low segment operation is striking, and this tendency is abundantly justified by the low mortality rate following this procedure. Thus, in the first series, the 31 low segment cases all lived, and in the second series, in 488 low operations the maternal mortality rate was 3.7 per cent.

TABLE VI. NONFATAL COMPLICATIONS

	FIRST SERIES	SECOND SERIES
Febrile morbidity (International Standard)	63.5%	61.3%
Pulmonary	9	14
Genitourinary tract	8	28
Acute dilatation of stomach	17	1
Postoperative convulsions (eclampsia)	5	1
Postoperative vaginal hemorrhage (2 deaths from this in first series)	3	3
Evisceration	1	4
Wound infection	11	15
General infection	8	18

Table VI lists the most important nonfatal complications. It is to be noted that the febrile morbidity is practically the same in both series. We were surprised to find that the figures in the second period showed little difference between the classical (63.8 per cent) and the cervical (62.3 per cent) operations. It was felt that the 17 cases of acute dilatation of the stomach in the first group (only one in the second) were in great part really instances of infection, probably peritoneal. The greater proportion of postoperative convulsions in Series I is simply a concomitant of the larger number of cases of eclampsia in this group. The fairly large number of cases of postoperative vaginal hemorrhage were thought to be due in some instances to uterine relaxation, in others to improper technique in suturing the uterus.

In Table VII, the causes of maternal death are listed. The maternal mortality rate was 16.1 per cent in the first series and 5.9 per cent in the second. A considerable part of this reduction is due to the fact that eclampsia has been almost eliminated as an indication. In each group, the mortality rates from peritonitis and septicemia were much too high, and we were greatly disappointed at finding so many in 1937, after pointing out in 1927 that one-fifth of the deaths were due to these two causes. In the second series, these complications accounted for one-third of the deaths. Seventeen of the 41 patients with eclampsia in Series I died, as did 9 of the 27 in the second series. It is to be noted that 3 of the 33 cases of placenta previa

TABLE VII. MATERNAL MORTALITY ANALYZED AS TO CAUSE OF DEATH

	FIRST SERIES	SECOND SERIES
Peritonitis	6	10
Septicemia	3	12
Ruptured uterus or scar	3	0
Toxemia	3	2
Eclampsia	16	7
Placenta previa	1	2
Pyelonephritis	0	1
Postoperative intestinal obstruction	0	1
Paralytic ileus	0	2
Postoperative shock	0	2
Spinal anesthetic	0	1
Antimony poisoning	0	1
Premature separation placenta	1	0
Acute dilatation of the stomach	2	1
Pneumonia	1	8
Postoperative vaginal hemorrhage	2	3
Heart lesions	2	4
Embolus	5	2
Moribund	0	1
Tuberculosis	0	1
Renal suppression	0	1
Doubtful	2	2
Total	47	64

in Series I and 7 of the 114 in Series II resulted fatally. One of the fatal cases of eclampsia in Series I and 2 in Series II were listed under peritonitis, as were 2 and 5 cases, respectively, of placenta previa. Pulmonary embolism caused 5 deaths in the first group and only two in the second. Two patients in the second series were moribund; one is listed as such, the other patient died of tuberculosis, and her condition was hopeless at the time of operation. These two patients were sectioned for the sake of the babies, both being saved. The case of antimony poisoning requires special mention. This patient was operated upon because of extensive granulomatous lesions of the vulva which precluded vaginal delivery. She was treated pre- and postoperatively by tartar emetic intravenously, and death was ascribed to hypersusceptibility to this drug.

In connection with the review of the maternal mortality, one significant fact was noted. In the first series, 23 of the 47 deaths occurred in patients whose records showed long labors, many examinations, attempts at vaginal delivery, membranes ruptured for many hours, etc. In the second group, these gross errors of judgment were noted in the records in only 11 of the 64 fatal cases. However, as 22 of these 64 deaths were due to peritonitis and septicemia, it is highly probable that the 11 additional patients had also been subjected to contamination from below. It would seem that more attention was paid to the matter of potential infection in the second series, but that none the less the bounds of safety were too often transgressed.

TABLE VIII. MATERNAL MORTALITY, ANALYZED ACCORDING TO TYPE OF OPERATION
FIRST SERIES

	TOTAL CASES	DEATHS	PER CENT
Classical Porro Not described	269	47	17.5
Low segment	31	0	0

In Table VIII the maternal mortality is analyzed according to type of operation. As noted above, the low segment operation, in the first series, was not followed by a single death, and in the second group the mortality after this operation was one-

half that following the classical. Of course, some of the latter may have been done in the more unfavorable cases, because of the greater speed and ease of performance; this could not always be deduced from the record.

TABLE IX. MATERNAL MORTALITY, ANALYZED ACCORDING TO TYPE OF OPERATION SECOND SERIES

	TOTAL CASES	DEATHS	PER CENT
Classical	545	39	7.2
Porro	39	4	10.3
Portes	2	1	50.0
Low segment	488	18	3.7
Not described	34	2	6.0
	1108	64	

In Table IX the fetal mortality figures are presented, classified chiefly according to the operative indications. When prematurity was the chief cause, the cases were listed under that heading rather than under the operative indication. In the first series 35 per cent and in the second 27 per cent of the fetal deaths were due to this cause. Of course, most of these were in the toxemic and hemorrhage cases; however, under these conditions it is doubtful whether vaginal delivery might not have been feasible.

TABLE X. FETAL MORTALITY

	FIRST SERIES	SECOND SERIES
Pelvic contraction	2	4
Eclampsia, term babies	4	0
Toxemia	3	1
Placenta previa, term babies	4	3
Premature separation placenta	3	3
Congenital malformations	4	3
Neglected labor	5	1
Ruptured uterus or scar	5	4
Tonic contraction of uterus	1	1
Cerebral hemorrhage	1	1
Uterine fibroids	1	3
Asphyxia	0	2
Pneumonia	0	1
"Stillborn," no details	0	8
Prematurity	19	31
Not stated	3	51
	55	117
Per cent	18.9	10.8

SUMMARY

From these two surveys we see that: (1) The incidence of cesarean section in New Orleans was 2½ times as great in the second period as in the first. Two questions naturally arise: Were too few operations performed in the first period, or were too many performed in the second period? Probably both questions can be answered to some extent in the affirmative. However, if 1.4 per cent is the correct figure for the Charity Hospital (it may be too low) to which many obstetric patients are referred because of complications, it would appear that 1.19 per cent for the total number of deliveries in the city is too high a proportion. The same might be said of the 2.87 per cent incidence of cesarean section in the private hospitals as a group.

2. The indications are more clearly set forth in the records of the past few years, and on the whole seem to be more judiciously placed in the second series.

3. The overstepping of the bounds of prudence in the second series was much less pronounced than in the first, but there is still much room for improvement.

4. The superiority of the low cervical operation is clearly shown.

5. The Porro operation should probably have been performed more frequently, as it is to be noted that 22 of the deaths in the second series were due to infection.

6. The newly developed technique for the performance of true extraperitoneal section should aid in further reducing the mortality.

7. The reduction in mortality rates (maternal and fetal) is gratifying, but both figures are still too high. We believe that there has been a further improvement since the presentation of this second report, but have not yet received the figures of the past three years.

8. It is felt that such surveys are of distinct value, especially when repeated every few years, and that such "stock-taking" benefits the profession in general and the obstetric specialists in particular.

REFERENCES

(1) New Orleans M. & S. J. **79**: 815, 1927. (2) Ibid. **90**: 731, 1938.

DISCUSSION

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—As Dr. King very clearly pointed out, the second study in the City of New Orleans showed a very great improvement over the first survey, and we feel sure that this would be true of other communities. In going over histories prior to ten years ago we found very indifferent histories as compared with those being taken today. Better histories bring improvement in diagnosis and more strict indications for cesarean section. Along with these improvements there must necessarily be improvement in operative technique as well as in the choice of operation.

By way of comparison, I desire to refer to a series done at the Methodist Hospital by one group of men, 18 in number, all trained along somewhat the same lines. The total deliveries were 27,234 in eighteen years. The total mortality was 3.18 per cent, which of course is very much lower than Dr. King's series, but to be expected from a selected group of men. This is neither the lowest nor the highest mortality rate for cesarean section done under the conditions under which this series was performed.

The fetal mortality in our series was 5.2 per cent. In Dr. King's first series, it was 18.9 per cent and in the second 10 per cent. The latter shows a vast improvement but is still not as low as it would be in a group of more highly trained obstetricians. Furthermore, it brings out the point that cesarean section does not necessarily guarantee a live baby, a fact not generally recognized.

Another study showed the general improvement attained by a specialized group working over eighteen years and shown in 3 six-year periods. The mortality rate steadily declined. Dr. King's study brought out this fact although not as strikingly. Furthermore, the superiority of the low-flap operation is strikingly brought out in our series as it was in Dr. King's.

Our indications for cesarean section run about the same as in Dr. King's series. This would tend to show that indications are fairly well standardized and if rigidly adhered to would undoubtedly reduce the present-day morbidity and mortality rates. Naturally, the competency of the operator and adequacy of the operating facilities will always be of prime importance.

More of these comparative studies should be made in order to keep the question of cesarean section, with its still relatively high mortality and morbidity, constantly before the general practitioner, and the general surgeon, as well as the obstetric specialist.

(The tables referred to will be found in the previously published paper by Matthews, Harvey B., and Aeken, Henry S., entitled "A Critical Survey of 1,066 Cesarean Sections," in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 38: 956, 1938.)

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—While repetition of a survey after some years affords interesting comparative material, yet it is my feeling that a cesarean section study should be continuous. We have tried to accomplish this in the City of Philadelphia by having hospital obstetric staff conferences meet at regular intervals in each hospital to discuss the current obstetric work.

In regard to their mortalities, the hospital conference is always asked to furnish its own opinion as to preventability and responsibility. Such a frank discussion in a local group tends to tighten up obstetric practice. Furthermore, continuous audit of cesarean deaths carried out before a large group of obstetricians in a city brings out the indications to which exception might be taken, the possible lack of prenatal study, errors in judgment, and technique on the part of the operator.

Although the incidence of cesarean section has increased to a certain extent in Philadelphia, we feel that the marked reduction in mortality in cesarean sections proves the benefit of the continuous review of obstetric surgery.

TABLE I. CESAREAN SECTIONS IN PHILADELPHIA

	1931	1932	1933	1934	1935	1936	1937	1938	1939
A. Total live births	33,773	32,093	29,228	29,751	29,988	29,652	30,059	30,739	30,232
B. Number of cesarean sections	601	591	583	638	703	799	811	795	857
C. Cesarean section rate	1.8	1.8	1.7	2.1	2.3	2.7	2.7	2.6	2.8
D. Cesarean section deaths:									
1. Classical	15	19	14	16	25	15	14	5	6
2. Cervical	4	6	3	4	6	4	5	1	4
3. Porro	1	0	0	0	0	3	1	1	0
4. Unlisted	18	11	6	1	1	6	0	6	1
Total	38	36	23	21	32	28	20	13	11
E. Cesarean death rate	6.1	6.0	3.9	3.1	4.6	3.6	2.5	1.6	1.3

DR. GEORGE KAMPERMAN, DETROIT, MICH.—I am greatly interested in this report because of a similar study made by the late Dr. Walter Welz in Detroit during 1925. His figures were appalling, for he found a maternal mortality of 13 per cent and a fetal mortality of 11 per cent. Since then Dr. Ward Seeley has made a comparative study of cesarean sections in Detroit during 1930 and noted a marked improvement. Five years after the report of Dr. Welz the maternal mortality had dropped from 13 per cent to 4.43 per cent (corrected 3.44 per cent). There had been no improvement in the fetal mortality, however, which was 12.8 per cent in the second report.

In analyzing the statistics it was interesting to see where the improvement had come. The low cesarean section which had in the meantime become much more popular seemed to have been partly responsible for a lower maternal mortality. But in my own mind I am not convinced that that was a great factor. We have become more conscious of the danger of cesarean section in the presence of infection, and that consciousness developed just about the time when we began to substitute the low cervical section for the classical section. It would seem that knowing when not to operate was an important factor in the improvement. More important still seemed to be the fact that eclampsia was no longer considered an indication for cesarean section, and I think this change was the chief cause for the improvement in maternal mortality.

DR. CARL HENRY DAVIS, WILMINGTON, DEL.—During the last year I have gone over the records of my private obstetric practice in Milwaukee, checking the results in various types of cases. I found a cesarean incidence of 4.8 per cent in the private group. At the Milwaukee County Hospital where we had our teaching cases, the incidence was 1.9 per cent. My fetal mortality in cesarean deliveries compares very closely with that of Dr. Matthews.

Curiously, I found in checking the temperature morbidity that in my classical cesarean sections there was a slightly lower percentage of morbidity (51 per cent) than in the low cervical cases (60 per cent), and that with the Porros, which were largely done in women who had had previous cesarean sections and wished to be sterilized, I had the most favorable morbidity rate of all, fever occurring only once in six cases.

I believe the reason for the improved results in my classical cases was that I have followed the same technique that we use in the low cervical operations, namely, to avoid the use of packs and to employ suction for removing fluid and blood. There was one death, due to an unrecognized postoperative appendicitis with ileus, in 73 cesarean sections. Cultures of the interior of the uterus were entirely sterile, so that I do not believe the patient died as a result of the cesarean section but as a result of the appendicitis.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—It is a self-evident fact that cesarean section has a minimal mortality rate only when there have been no antecedent medical complications or obstetric difficulties. Contracted pelves or true disproportion alone of all obstetric indications gives cases with this minimal operative risk. With all other indications there is a dual hazard, the operative risk and the danger inherent in the indicating complication.

Of course, the unindicated or "expedient" operations on healthy women will be followed by a negligible mortality rate. Therefore, the man who holds himself to strict indications for cesarean section will always have a definitely high mortality rate. It is just as irrational for the obstetrician to mass all his cesarean sections irrespective of the indications as it would be for the abdominal surgeon to so group all his laparotomies.

Figures on cesarean section garnered from 335 hospitals in 1929 showed that 292 women died following 4,889 sections, a rate of 5.97 per cent. I showed the table to the actuary of one of our largest insurance companies. His first query was, "How many hospitals had no cesarean deaths? As you are dealing with the problem of cesarean mortality, it is improper to include the hospitals which lost no mothers." The table was therefore revised. In 161 hospitals, there were 1,625 operations without a maternal death. Therefore, in 174 institutions there were 3,264 operations with 292 deaths, or 8.95 per cent. Of these, 29 hospitals had 1,269 operations with the loss of 42 mothers, 3.3 per cent. The remaining hospitals, 145, had 1,995 sections with a mortality of 12.5 per cent, which constituted 31.3 per cent of all puerperal deaths. Again, in 97 (55.7 per cent) of the 174 hospitals with a mortality, 161 deaths occurred, or 20.7 per cent. In 18 hospitals with 43 operations 35 mothers died, or 81.4 per cent.

I presented to certain authorities the interesting fact that as the numbers of annual births decreased in hospitals the cesarean mortalities rapidly increased until in 7 with 8 operations no mothers survived. Most men agreed that the men in those hospitals neither knew when or how to perform the operation. One gave a different explanation. "In those small hospitals the operations were performed on necessitous indications. In our clinic we carefully select the cases and the majority of the operations are dictated by expediency."

I imagine that most of the decline of mortality in New Orleans was due to the elimination of eclampsia as an indication. How much of this decline also is the result of a prohibition of sections being performed by general practitioners? In northern hospitals where such a ban is in vogue, the incidence of cesarean has fallen and the mortality rate has declined.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—I am particularly interested in the discussion of the relative virtues of the low cesarean section as compared with the old classical operation, and I am in a peculiarly favorable position to determine which

is the better. I have to read long galleys for the Year Book every year, in which is presented to me a digest of the literature on obstetrics all over the world. The impression I get is that the old classical operation should be pronounced obsolete. From the Year Book pages, there is a continual succession of statistics showing the greater safety, even in the hands of the modern general surgeon, of the low cervical operation, which gives better results for clean as well as infected cases.

The mortality statistics of Dr. King agree with those I get from the literature and those of Dr. Holmes fit very nicely into the picture also. I believe that the rates of the abdominal delivery are so high that the medical profession will have to do something about it. If we doctors do not do something to improve the conditions under which women have babies, either the public or the Government will, and it is time for us to clean our own house first.

DR. FREDERICK H. FALLS, CHICAGO, ILL.—The point I wish to discuss is the difference between the results obtained in the low cervical and the classical cesarean section. There is only one way to decide the matter and that is for one operator to do both operations in alternate cases. In our clinic I have just completed 200 cesarean sections, and every other one has been done by the classical alternating with the low cervical. The operations were performed in the same room. I opened and closed the skin personally. The same nurses and interns were in attendance, and the patients received the same preoperative and postoperative care. The result of the study is that, so far as I can determine, there is practically no difference between the two operations.

In analyzing the amount of postoperative distress, one-twelfth of a grain more of morphine was used to keep the patients who had classical cesarean sections comfortable than was used for those who had low cervicals.

We had two deaths, one of which was not due to the operation. As in Dr. Davis' case, the wound was perfectly healed but the patient died of a chronic nephritis, which was the reason for the operation. The other was an infected case in which the patient died of the infection. We feel that the evidence from this series for the low cervical is not very strong and in the hands of the same operator about the same results will be obtained.

DR. FRED L. ADAIR, CHICAGO, ILL.—In the first place, I do not believe that cesarean section in itself is a particularly dangerous operation if the operator is competent and the cases are properly selected. Any maternal mortality in excess of 1 per cent and any fetal mortality in excess of 2 per cent is too high. While the indications for cesarean section have changed, the contraindications have not changed materially. The excessive mortality in most hospitals is due not so much to an extension of the indications as to the neglect of enforcing the contraindications for this operation. In any institution, the obstetric staff together with the hospital authorities should see to it very definitely that the contraindications are very closely observed with regard to cesarean section. That is the safest way to keep the mortality within proper limits.

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—I very recently made a survey of 343 cesarean sections in my own group, consisting of seven men, all of whom were teaching in Northwestern University. In this series of cases in which the contraindications had been very closely observed, we had a mortality of 0.88 of 1 per cent. Hence, under favorable conditions I think the operation can be carried out with a high degree of safety.

DR. KING (closing).—There is a much larger percentage of cesarean sections performed in hospital practice than in private practice. For instance, we had 1.14 per cent of cesarean sections in all deliveries in New Orleans, and 2.8 per cent of the hospital deliveries were by cesarean section. The series of others give us about the same figures.

Improvements must also be considered as partly due to dilution of the figures. Thus in the first series 1 out of every 204 babies was born by cesarean section, whereas in the second series this proportion was increased to 1 out of every 86.

Thus it is apparent that many more favorable cases were included in this second series. That naturally helps us to bring down the mortality rate.

It appears that the low section is the preferable operation as shown by our figures as well as by others, and, of course, the results are better, because the low sections were practically all done by specialists. Dr. Falls states that he obtained as good results from classical as from low sections. All of his cases, however, were either elective or the patients were operated upon early in labor, and under such circumstances equally good results, after the two types of operation, are to be expected. In the patients who have been in labor for some time I feel that it is well established that the low operation will give the best results. Again we must not overlook the subsequent obstetric history of these patients, for I feel that it is well established that rupture of the scar is more frequent after the classical operation.

There is no question that the selection of the cases is of vital importance. The mortality rate of the obstetrician is low, not because the specialist is a better operator than the general surgeon, but because he avoids the infected cases and selects those patients suitable for cesarean section. Note that one-third of the deaths of the second series was due to septicemia and peritonitis. This proportion would have been much lower if the proper selection of patients and operation had been more carefully practiced. The situation as regards eclampsia was much improved in the second series. In the first series there were 41 cases of eclampsia with 16 deaths, which amounted to one-fourth of the total fatalities, whereas in the second series there were 27 cases and 7 deaths.

The Committee has recommended that all hospitals in New Orleans adopt the procedure of requiring a consultation for all cesarean sections. However, some of the private hospitals have not come to that point of view.

PSEUDOHERMAPHRODISM*

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HUMAN interest is attracted by the unusual. Formerly hermaphrodites were curiosities who found it difficult to establish a satisfactory and useful place in society. These unfortunates being neither male nor female were buffeted from one classification to the other, often becoming social outcasts in spite of their keen mentality. Development of genetics, embryology, biology, and endocrinology has benefited these misfits, and study of the hermaphrodites has added to our knowledge of these sciences.

Hermaphrodite is an ambiguous term which originated with the ancient Greeks. A child born to Aphrodite and Hermes possessed the sexual attributes of both father and mother. Appearing to be a combination of both, it was called "Hermaphroditos." Hence, hermaphrodism signifies a combination of male and female in the same individual.

True hermaphrodism exists when the same individual bears both male and female gonads and is capable of impregnating a female and of being impregnated by a male. This state is characteristic of many lower form of animals, e.g., the earthworm. Its occurrence in man is exceedingly rare.

Young[1] cites Photakis as asserting positively that such classical hermaphrodism has never occurred in man in contrast to Neugebauer's citation of ancient literature where the tragedy and comedy of true hermaphrodism were recorded. Omitting the proof of ability to impregnate or be impregnated as essential to true hermaphrodism, Young[1] collected reports of 20 cases proved microscopically. Five had an ovary on one side and an ovotestis on the other; 4, a testis on one side and an ovotestis on the other; 3, an ovotestis on one side and the character of the gonad on the other side undetermined; 6, an ovotestis on each side; and 3, a testis in the scrotum on one side and an ovary in the pelvis on the other.

Pseudohermaphrodism exists when gonads of only one sex are present, but the appearance of the rest of the genital organs does not clearly indicate the true sex. Several classifications have been prepared to express the numerous combinations found. Since no two cases reported are alike, detailed terminology becomes complex. It is simpler to classify according to the nature of the gonad.

During the past three years, I have been one of a group to observe three male pseudohermaphrodites. The only characteristic belonging to all three cases was the presence of male gonads.

Case 1.—E. W., aged 17 years, first seen June 30, 1937, complained that she was a hermaphrodite and wanted to know what could be done to make her more like a girl. In general, the patient had been healthy and had never experienced any

*Read at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

serious illness. She was born in East Prussia. At birth the doctor told the family that she was a female child though not quite normal. When the child was four months old, the family moved to Essen. When she was a year old, her parents consulted a gynecologist in Königsberg. He said that she was an abnormal female but should wait until the age of puberty before anything was done. When she was 4 or 5 years old, they saw other doctors in Germany who likewise advised waiting until puberty. When she was 5 years old, her family migrated to America. They consulted several physicians in this country who likewise advised postponing any

Fig. 1.

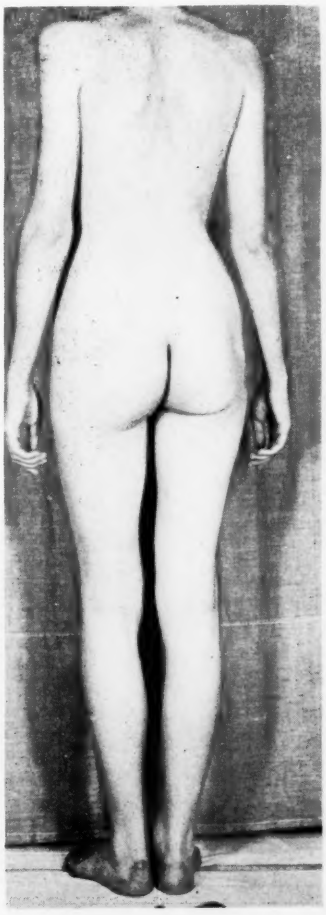

Fig. 2.

Fig. 1.—Case 1. Front view, preoperative. Shows feminine pubic hair, scrotum, previous laparotomy scar, female breasts, and masculine extremities.

Fig. 2.—Case 1. Rear view, preoperative. Shows female pelvis, narrow waistline, and masculine extremities.

operative procedure until puberty. During childhood her family considered that she was distinctly feminine in appearance and in behavior. At the age of 12 she consulted another physician who likewise advised waiting. When she was 14 years old, a laparotomy was performed. Rudimentary organs were found "all messed up together." No uterus was present. The operator thought that there might have been a rudimentary vagina. The appendix was removed at that operation. She was given some sort of pituitary preparation by injections with no apparent effect. Erections of the clitoris began at the age of 10. She had noticed that when

the clitoris became erect, it always curved downwards, the curve being exaggerated by erection. About one-half teaspoonful of material was obtained by masturbation. Nocturnal emission occurred about once in two weeks. She considered the structures in the scrotum to be testes because she had obtained semen from the vagina (urethra) (Figs. 1 and 2).

Examination, when she was first seen on June 30, 1937, showed a tall, lanky individual of light complexion. Her extremities, hands and feet, were long; height was 5 feet, 9½ inches; weight was 135 pounds. The light brown hair was slightly curly. Hair distribution was mixed, masculine and feminine with feminine distribution of pubic hair. Development of fine hair on the limbs was conspicuous. Development of the hair on the face suggested a masculine tendency. Considerable acne marred the face and back. The light gray eyes showed normal reactions and

Fig. 3.—Case 1. Preoperative. Shows saddle scrotum and rudimentary penis.

movements. Nose was relatively large and pointed. Teeth were normal. No general glandular enlargement was noted. The thyroid cartilage was prominent. Heart and lungs were normal. Pulse was 80 and blood pressure 120/78. Reflexes were active. A midline laparotomy scar appeared below the umbilicus.

Skeletal Development.—The bones of the extremities were long and heavy. The spine was straight. The hips were broad and the pelvis was feminine.

X-ray Examination.—The sella turcica was normal in size and shape. The bones of the skull were normal. The pelvis was rather large, but the sacrum was somewhat lower between the ilia than is ordinarily the case in a woman's pelvis. The epiphyses at the knees were closed, and the epiphyses of the radius were only recently closed though still visible.

Rapid development of the scrotum and contents noted at the age of 9 had continued to increase. The saddle scrotum contained a gonad on each side. The wrinkled skin over the scrotum was deeply pigmented. The erectile organ 4 cm. long, curving downward, resembled a penis with a dimple at the tip representing the meatus. The urethra opening at the base of the penis was thought by the patient to be a miniature vagina. The voice was high contralto. The breasts, de-

veloped more than would be expected for a male and less than for a female, showed definite ducts opening on the nipples. A rudimentary prostate was felt on rectal examination (Figs. 3 and 4).

Examination by Dr. Cothran, July, 1937: "The penis appears to be about normal size for a boy of 7. The foreskin is well back off the glans and could be considered as labia minora. The opening of the urethra is in a position which would be comparable to the penal-scrotal junction in a normal male. The scrotum is almost completely divided in the midline. Gonads are about normal size for the age of 17. The vas can be palpated.

"*Cystoscopic Examination.*—The bladder capacity is normal. The bladder wall is normal with the exception of an area around the neck over the lower trigone where there is a moderate amount of acute but low grade inflammatory reaction. The urethral orifices are in normal position. The urine shows a few pus cells (cultures were negative). There is no elevation at the base of the bladder which

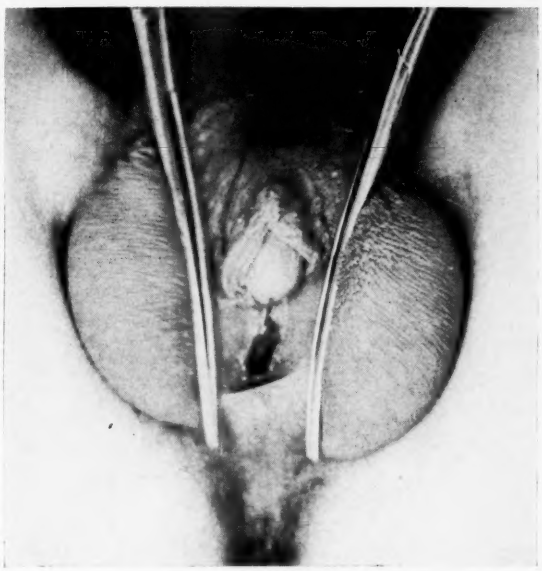

Fig. 4.—Case 1. Preoperative. Shows urethral opening at penoscrotal junction; dimple representing meatus on rudimentary penis.

would suggest the cervix pushing in. The bladder sphincter seems to work well. In the posterior urethra is a structure which is apparently a verumontanum. The small prostrate is massaged and a small amount of clear fluid obtained. This contains 10 pus cells per low-powered field."

Laboratory studies showed normal urine; blood Wassermann, negative; hemoglobin, 90 per cent; red blood cells, 4,850,000; sodium, 342; chlorides, 453; cholesterol, 196; albumin, 4.37; and globulin, 1.52. Glucose tolerance test revealed a delayed utilization of sugar and a phosphorous curve obtained when insulin is lacking. Three basal metabolic rates were within normal limits. The temperature at all three readings was subnormal (97°, 97°, 96.4° F.). The respiratory quotients were 0.82, 0.79 but dropped to 0.77 one-half hour after the administration of glucose. Hormone studies showed no estrogens or androgens in a single specimen before operation. The dilution was too great to give a positive test.

Operation.—Aug. 10, 1937. Transplantation of gonads from scrotum into the abdomen. An incision was made over the right inguinal canal, opening the extraperitoneal space. On opening the cremaster a cord containing vessels and vas was exposed. This cord extended upward from the gonad, passing through the inguinal canal into the retroperitoneal space toward the midline at the base of the

bladder. The tunica over the gonad was incised for inspection of the gonad. There seemed to be a well-defined epididymis between the testis and the vas. Careful inspection of the gonad showed a smooth surface. Two hydatids were seen on the upper pole (Fig. 5). No structures resembling a corpus luteum were seen. A few areas were suggestive of Graafian follicles. If the gonad were an ovotestis, the distribution of the tissues must have been intimately mixed. On inspection there was no portion of the gonad which appeared distinctly different from the rest of the structure. A very small piece of the cortex was excised for microscopic study. In order to prove the structure of the gonad, it would be necessary to remove one entirely or to take a section the full length of the gonad. This did not seem justified. The gonad together with the vas was dropped into the retroperitoneal space and the incision closed in the usual manner for repair of a hernia. On the left side the same procedure was carried out except that the whole tunica was removed and carried with the gonad to the retroperitoneal space. There was ample room for the gonads in the retroperitoneal space. They were well protected in this position. This operation was done for the purpose of permanently elevating the temperature of the gonads in order to diminish their testicular function and to permit the scrotum to collapse, thus appearing more like labia. Postoperative course was uneventful.

Fig. 5.—Case 1. At operation. Shows structure like a testis, hydatids, vas and spermatic vessels ready to transplant into hernia incision.

Following the operation the pigmentation over the scrotum diminished. The tissues shrank so that it became possible to do a plastic to reconstruct the tissues to resemble labia instead of scrotum. Following the operation the breasts enlarged. The clitoris or penis remained the same size. The possibility of erection and of masturbation was still retained, though almost no fluid was obtained by masturbation. The voice seemed a little lighter in quality and her family were convinced that it was more feminine. The hair on the face continued to be a source of great annoyance. Electrolysis was tried but without great satisfaction. Patient has since resorted to a depilatory.

Plastic operation for construction of labia and covering of clitoris or penis was done on Aug. 8, 1938: An incision was made in the midline between the saddle scrotum; the raw areas were brought together across the midline to increase the amount of tissue resembling a mons veneris. The redundant foreskin was adjusted to cover the penis or clitoris. This was nearly hidden by the tissue. The urethra still opens underneath the erectile organ. At the same time the broad scar from the patient's former laparotomy was excised to make a more sightly scar (Fig. 6).

The patient became satisfied with her state after the two operations and felt that she could go among other girls in the locker rooms and gymnasium without hesitation. Her behavior became more and more feminine. A normal interest in

boys developed. Before the operation she hesitated to test herself for fear that if she gave way to her inclination to go out with boys she might be disappointed and all would be lost. She was greatly relieved when she found that she had a normal reaction to the company of young men.

*Hormone Assays.**—"Urine samples 3-18-40, representing two days' collection of urine, and 4-1-40, representing 4 days' urine, were assayed for androgenic activity by the castrate rat method and for estrogenic hormone by the Allen-Doisy method.

"Both samples gave a negative estrogenic reaction when tested at 40 I.U. and 25 I.U. per day levels, respectively; that is, they contain less than 40 I.U. and 25 I.U. per day equivalent or less than 80 I.U. per sample.

"Sample 3-18-40 gave a weakly positive androgenic response at 25 I.U. and negative at 50 I.U. per day equivalent.

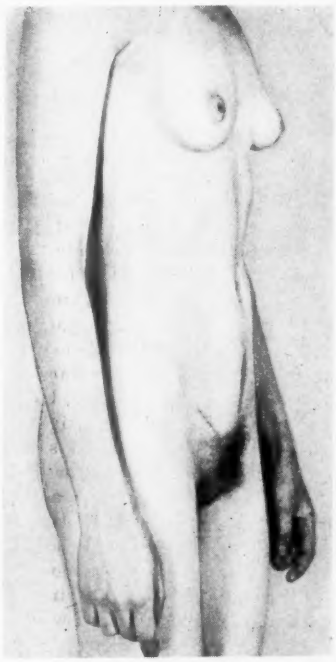

Fig. 6.—Case 1. Postoperative. Shows enlarged breasts, and scrotum converted to resemble labia.

"Sample 4-1-40 gave a negative response at 25 I.U. per day equivalent or 100 I.U. in the whole sample."

Personality.†—"During our first observations and examinations of this patient between June 30 and Aug. 10, 1937, we were always impressed by a particular type of demeanor. Here was an individual in woman's attire. When addressed, she immediately reflected a guilty apprehensiveness which carried in it the implication, 'I'm masquerading; I'm not what you think I am.' To us, her deception was less clear than her reflection of culpability. After several office visits, this implication of moral turpitude gave way to a representation of intellectual alertness. She was keenly interested in the details of her intelligence tests, as carried out by Dr. Schott, and she was rightly pleased when he evaluated her at the Superior Adult Level, with an I. Q. of 139, with her chronologic age at 17 years and 7 months. Her instinctive urges and affective cravings seemed poorly formulated except for

*Assays of urine by Dr. D. A. McGinty.

†Personality observation by T. J. Heldt, psychiatrist, and E. L. Schott, psychologist, Henry Ford Hospital.

one motivating drive: 'Lately, I had a sex dream in which I was playing the female part; it made me decide I was going to do something about it, and that's why I came to the doctor.' The patient's mood changes were of adolescent type, with a rather strong tendency to the reflective and introspective side. Her estimate of herself was at low ebb. Her adaptability to social demands and to her environment generally was very good. The dynamic nature of her personality organization may be judged from the fact that she was the president of her class, the business manager of the school paper, the manager of the school secondhand store, and member of several honor societies. Her conduct and deportment were, at all times, acceptable. Her responses to standard tests are informative. Dr. Schott reported the following: On the Thurstone Personality Schedule, she made a total point score of 65, indicating some degree of emotional maladjustment. On the Northwestern Introversion-Extroversion Scale, she made a total point score of 618, which is slightly above the midline toward the extroverted end of the scale and very significantly on the Terman Masculinity-Femininity Test, she made a total point score of 'plus 28, which, when compared to the norm for high school juniors (patient has just finished junior year in high school) is more masculine than 95 per cent of girls, and as masculine as approximately 20 per cent of the boys of junior standing in high school.'

"On Aug. 10, 1937, the patient had her first gynecologic operation. Psychologically, there immediately set in a favorable metamorphosis of her personality. Endocrinologic factors probably added their part shortly after. For the next year, we watched the gradual disappearance of the patient's guilty feeling of deception, and saw her keenly looking forward to her plastic operation by Dr. Pratt on Aug. 9, 1938. Shortly after, she openly declared herself a female who could pass general inspection. These self-found assurances soon registered the disappearance of excessive self-consciousness to a point where re-examination was postponed until the recent months, February to May, 1940. That she has become progressively more feminine is clearly evident in patient's spontaneity and initiative toward all manner of things of feminine interest. Questioning, both direct and indirect, brings answers that need no discounting. Although it might be said that much of patient's personality is conceivably due to purposeful striving and constant training, yet we cannot escape the fact that the motivation for such striving arises within the same individual who was previously so gropingly masculine. Standardized psychologic determinations are now reported by Dr. Schott as follows: Re-evaluation of the patient's intellect during February again gave her a very superior rating, with an I. Q. of 146 (chronologically, 20 years, 3 months). On the Northwestern Introversion-Extroversion Test, she made a total point score of 605, 'which is very close to the midline of the scale, or just 5 points toward the extrovert end. This is very close to her previous score of 618.' On Terman's Masculinity-Femininity Scale, now very significantly, in comparison to the norms given by Terman for sophomore girls in college, gives patient a rating of –116, which is in the fifth percentile for college sophomore girls; and being thus to the minus side means that the patient now rates as feminine as 95 per cent of the women in her group. This is essentially a full reversal of her previous showing on this same test.

"The patient aspires to additional educational attainments, and understandingly hopes that marriage may not be denied to her."

CASE 2.*—E. K., aged 15 years, first seen Feb. 13, 1937, complained of a left inguinal hernia which had been present since birth. In earlier years of life there was an umbilical hernia which disappeared spontaneously. Six days before admission the patient complained of a sharp attack of pain in the left inguinal region associated with some vomiting. He was away at school. The school physician who examined him stated that the hernia was partially strangulated, but it was reducible by manipulation. A truss was advised until vacation. For several years the patient had noticed a mass descending into the left scrotum on straining, but it had always been reducible.

*This case is presented through the courtesy of Dr. W. W. Noel, formerly of the Surgical Staff of the Henry Ford Hospital, now of Henderson, N. C.

Positive findings in the past history were measles and influenza without complications; mastoidectomy at the age of 7; indefinite history of urticaria, hay fever, and asthma. There was a history of frequent colds and sore throats.

General physical examination showed a well-developed boy of 15; height 5 feet 10½ inches; weight 160 pounds. He showed a normal masculine development. The body contour was distinctly male. The penis was normally developed. Distribution of hair was masculine. No enlargement of the breasts was noted. No general signs of feminity were observed (Fig. 7). Left maxillary sinus was slightly cloudy. Examination of the heart and lungs was normal. Blood pressure was 105/65. No masses or tenderness in the abdomen was demonstrated. Skeletal development was normal. The features of the face were rather fine. There was no suggestion of a beard. He had done well in school. Examination on admission showed a complete left inguinal hernia, but the right scrotum was empty. Palpation of the right inguinal

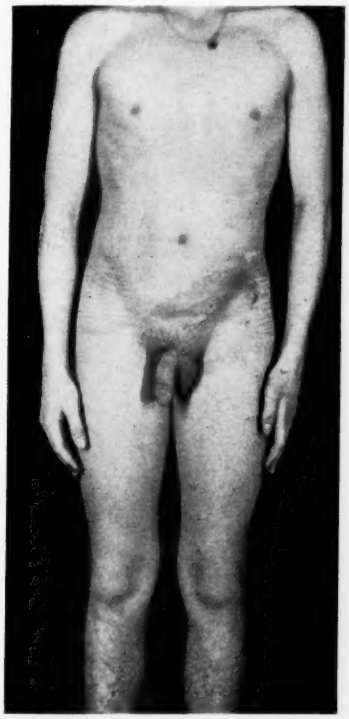

Fig. 7.—Case 2. Postoperative. Shows normal male torso, extremities, and genital organs. The discoloration of lower abdomen and groin is due to antiseptics and dressings for operation.

canal suggested the presence of an undescended testis. Otherwise the examination was essentially negative. It was noted that the voice was somewhat high-pitched; some slight suggestion of feminine behavior, though nothing definite, was stated.

Rectal Examination.—Prostate was small, but no seminal vesicles could be palpated. The pubic hair showed a feminine distribution. The boy had noted frequent erections during the past two or three years. There were nocturnal emissions as often as once every two weeks. He admitted masturbation but not excessive. He preferred the company of males, but appeared to have a normal male reaction to females.

Laboratory Findings.—The blood Wassermann was negative; hemoglobin, 88 per cent; and urinalysis, normal. No hormone analyses of urine were made in this case.

Operation.—Radical repair of the left indirect inguinal hernia was done by Dr. Noel on Feb. 18, 1937. The structures of the inguinal canal showed nothing unusual. At the time of operation the hernia sac was empty. The left testis was brought into the incision by traction. The testis was not accompanied by an epididymis. The vas deferens was small and poorly defined. The vas was lying between layers of peritoneum close to a structure that proved to be a uterus. When the uterus was brought into the incision, it resembled a normal uterus in contour, the size being below normal for the age of 15. Tubes were present, and the gonads were in the usual relative position of ovary to tubes. A cordlike vas, which seemed to fray out in the broad ligament, was present on the right side but did not communicate directly with the gonad (Fig. 8). The gonads were dissected from the uterus and tubes. The right gonad was dropped back into the peritoneal cavity, the raw areas having been covered with peritoneum. The left gonad was brought down into the left side of the scrotum. A section was taken from the gonads for microscopic examination. The uterus, tubes, and a portion of the vagina were excised. The vagina extended downward, penetrating the peritoneum. Apparently, it ended at the urogenital fascia. A greater portion of the vagina was excised with the uterus. The postoperative course was uneventful.

From the time of the operation in February, 1937, to November, 1937, his height had increased to 6 feet and his weight to 180 pounds. His masculine appearance increased. There had been an increase in the growth of body hair.

Pathologic Diagnosis.—Male reproductive system: infantile testis and epididymis; rudimentary uterus, Fallopian tubes and cervix, hermaphrodism.

Fig. 8.—Case 2. Taken at operation. Shows uterus, tubes, and gonads exposed through a hernia incision.

Tissue consisted of uterus, tubes, vas deferens, and gonad found in a fifteen-year-old male.

The specimen consisted of an irregular mass of soft fibrous tissue covered mostly by a thin endothelial tissue. This resembled somewhat an underdeveloped uterus. On either side rudimentary Fallopian tubes projected. These tubes had no demonstrable lumina. The "uterus" was a muscular tube with a soft mucosal surface 1 to 3 mm. in thickness. Another flat plaque of tissue with a soft mucosal surface was also present.

Microscopic: Section through the testis and epididymis showed small tubules with no active spermatogenesis. Very little mitosis was noted within the lining of the seminiferous tubules. The interstitial cells were quite large in the sections examined. The epididymis was essentially normal.

Sections through the vas deferens also appeared normal.

Section through the structure which was grossly identified as uterus showed the character of an infantile uterus in which there was a tall, columnar, epithelial lining with several irregular glandular structures in the mucosa. The stroma of the mucosa was rather fibrous. Muscle fibers were abundant throughout.

The Fallopian tubes showed a number of villous processes and also were surrounded by muscle fibers.

Portions of the plaque of tissue (vagina) removed from the pelvis showed a covering of a single layer of tall columnar epithelium with considerable amount of mucin. Mucous glands were noted in the stroma which in addition contained muscular fibers and fibrous tissue.

CASE 3.*—G. K., aged 20 months, was seen on July 29, 1937, as an emergency on account of a strangulated, left inguinal hernia. The child had been previously observed at the age of 17 months for acute suppurative mastoiditis, tonsillitis, and pharyngitis. A mastoidectomy was done May 6, 1937, which healed completely in about one month. Tonsillectomy and adenoidectomy were done June 4, 1937, from which the patient promptly recovered.

At the time she came to the hospital for the mastoiditis, she was wearing a truss for bilateral inguinal hernia which was said to have been congenital. The parents were advised to have the hernia repaired. The patient was taken to the country to recuperate following the mastoidectomy and tonsillectomy. She was readmitted as an emergency on June 29, 1937, because the left hernia had become strangulated. The symptoms present were swelling, pain, and vomiting. The parents had been warned of the possibility of strangulation; therefore, they came promptly for attention.

Physical Examination.—The patient was a light blond with curly, flaxen hair. The examination was summarized by "a normal female infant." Weight was 24 pounds.

Operation by Dr. Lam, July 29, 1937: The left inguinal canal was opened. The mass in the canal had been partly reduced by relaxation under anesthesia. Cloudy fluid was noted in the hernia sac on account of the strangulation. Since the child had a normal external appearance of a female, the operator was much surprised to find a vas deferens, rudimentary testis, and epididymis. The structures were removed. The intestine recovered its tone and no operative procedure was necessary for it. The hernia was repaired.

Operation on August 3, 1937: Repair of right inguinal hernia. The structures in the inguinal canal were incised. On opening the cremaster a rudimentary testis, epididymis and vas were found, quite similar to the ones which had been previously removed from the left side. They were placed extraperitoneally under the transversalis fascia. The hernia was then closed. The pelvis was explored and no evidence of uterus, tubes, or ovaries was found.

Microscopic sections were reported by our pathologist to be those of infantile testis, epididymis, and vas deferens of normal structure, showing no pathologic change. Postoperative course was satisfactory. Patient has not been observed since then.

DISCUSSION

The three cases reported are classified as male pseudohermaphrodites, because in each instance the gonads were testes. In Case 1 there may be a possibility of true hermaphrodism on account of a suggestion of Graafian follicles seen by gross inspection, but this observation was not supported by microscopic examination. The excretion of sperm established the existence of testes.

Endocrine studies of pseudohermaphrodites would be enlightening, but, unfortunately, only a few have been reported. Hearty cooperation of the patient in Case 1 permitted complete investigation, while Cases 2 and 3 were discovered at operation and special studies were limited because neither the patients nor their families were aware of the true condition.

The minimal findings of sex hormones in Case 1 are not consistent with the development of the individual. Theoretic speculation might

*This case is presented through the courtesy of Dr. C. R. Lam of the Surgical Staff of the Henry Ford Hospital.

assume that in the absence of a uterus the hormones are utilized in a different manner than in normal individuals; that the hormones have been present in larger quantities in the past but at present are minimal; that the balance of the hormones causes their destruction in the body so that they are not recovered in the urine.

An attempt to estimate the hyper- or hypofunctions of the other glands may be questionable, but if one can be permitted to interpret the findings of blood chemistry, it might be assumed that there were mild degrees of hypothyroidism, hypoinsulinism, and mild grades of overactivity of the pituitary and adrenal cortex. Many of the physical characteristics are consistent with the overactivity of the pituitary or adrenal cortex. The blood pressure-raising principle of the adrenal medulla has not been in excess. There was some apparent interference with normal utilization of glucose which might be due to pituitary antagonism or insulin lack. The interpretations of the function of these are largely speculative.

A prolonged discussion of the biologic, embryologic, and genetic relations is not possible here. These special fields are ably presented by Young[1] in his monograph and by the authors of several chapters in *Sex and Internal Secretions.*[2]

The social status of pseudohermaphrodites is a matter of prime importance. The study of our three cases by a group resulted in no unanimity of opinion as to what should be done with them. In Case 1 the majority felt that the individual should be transformed as much as possible to the female type; the opposite view was held by the minority. In Cases 2 and 3 the operators felt that the patients' best interests were preserved by not telling them or the family of the true conditions. The majority group opinion was against this and probably will prevail. It would seem that the judgment of the psychiatrist should be given a great deal of weight in any consideration of the treatment of pseudohermaphrodites. Following is a comment by Dr. Heldt:

"These pitiful individuals are more nondescript in their own feelings than they are on physical inspection. Although they have the right to the best that science has to offer, they are often shunned, socially ostracized, and avoided, if not maligned, by layman, surgeon, and physician alike. The foregoing cases clearly illustrate the fallacy of such an attitude. It is probably not so much surgical courage that is needed as it is sociologic understanding. The surgeon hesitates to undertake plastic operations on these individuals lest he be open to malpractice suits. Such suits are too often born of the greed of some poorly qualified attorney and the abject ignorance of the public. These cases are not as rare as you may think. Every psychiatrist can point to several during the course of his years of practice. Here are two: An individual in his forties with ample penile organ, but small scrotal contents for years masqueraded as a woman cook in city hotels. His sparse barba permitted him to let his hair grow long in imitation of a woman. All his feelings, attitudes, and desires were feminine. During recent years, because of his fear of "being found out," he has been compelled to dress as a man. He is very miserable. In the privacy of his own room he lives the life of a woman. Repeatedly, he has beseeched physicians and surgeons for a plastic operation to convert him into a woman. He has always been denied. Another individual, late in his thirties, has a liberal penile organ, apparently rudimentary testes, but withal, large and pendulous breasts. Because of same, he is forced to dress as a woman and to live

the life of one. However, all of his feelings are those of the male. Due to his pseudo-rôle as a woman, his fears have ostracized him to the point that he avoids the medical profession.

"The case of E. W. here reported by Dr. Pratt discloses the value of surgical and medical assistance. Psychiatrically, it is judged that more than 60 per cent of E. W.'s transformation is due to the patient's alteration in mental attitude and personality organization upon a background of objective alteration granted her through surgery. It is judged that only a small 40 per cent can be credited to any estrogenic hormones that might be present. Rich though this field be in satisfaction for the plastic surgeon, it is greater still in its humane implications."

REFERENCES

(1) *Young, H. H.:* Genital Abnormalities, Hermaphrodism and Related Adrenal Diseases, Baltimore, 1937, Williams & Wilkins Company. (2) *Allen, E.:* Sex and Internal Secretions, Baltimore, 1939, Williams & Wilkins Company.

DISCUSSION

DR. ROBERT A. ROSS, DURHAM, N. C.—There are two classes of pathetic individuals who have benefited by the newer knowledge showing the bisexual qualities of the individual, namely the pseudohermaphrodite and the sexually perverted. There is no doubt that both classes have been somewhat mistreated in the past. Often the pseudohermaphrodite has been subjected to early damaging surgery simply to confirm a diagnosis, the activating motive more than likely being curiosity rather than surgical judgment. Irreparable harm may be done by such unwise procedures.

That Dr. Pratt resorted to psychiatric consultation is not surprising and the value of this move is evident. Painstaking effort was made to find out what the individual desired and what sexual path offered more hope. In the past, the opposite was often true. The operator and family usually made the decision for the individual and the resulting agreement sealed the decision.

We regret, with Dr. Pratt, that complete hormone assays could not have been done. However, in view of other studies on individuals of this age it appears quite doubtful if these would have been conclusive. Until we know more about the source, utilization and metabolism of the androgens in the female, one could not interpret such results critically. For the same reason it would seem wise to withhold the androgenic products as therapeutic agents in the female.

We have treated surgically two pseudohermaphrodites at Duke Hospital in the past five years. One was quite similar to Dr. Pratt's first patient and in this case our results have been entirely satisfactory. The other patient was a "man" who was small and psychically derelict when we first saw him. The social agencies, the police court, and the family were anxious to have "him" converted into a "male." Plastic operations on the clitoris and scrotum created fair external genital organs, but also created intense resentment. The subsequent course has been one of continuous lawlessness, meanness, and intractability. The individual undoubtedly really wanted to be and should have been helped to become a female.

Dr. Pratt's thorough case studies point to the fact that these individuals should have sympathetic and prolonged handling before surgical procedures are elected. His paper offers two distinct contributions, the utilization of the body heat in the abdomen to diminish the male gonad function and the consultation with the psychiatrist early in the treatment.

DR. E. L. KING, NEW ORLEANS, LA.—Did this girl have anything like a vagina and was any attempt made to obtain fluid after operation to ascertain if it contained spermatozoa?

DR. EMIL NOVAK, BALTIMORE, MD.—The external sex characteristics in these cases of pseudohermaphrodism are likely to be of little value in indicating the nature of the gonads. With pretty much the same external sex characteristics, one may find either a male or female gonad.

A case which I reported some years ago is very similar to that presented by Dr. Pratt this morning, except that the cryptorchidism in my case already existed, while in Dr. Pratt's case it was surgically produced. My own patient exhibited typical female psychology and libido, although her only gonads were testes. There was no vagina, and later I constructed a satisfactory artificial canal. In my own case the heterosexual gonads were removed, although, were I to encounter a similar case now, they would probably be left. We are getting away from the idea that the male sex hormone is diametrically antagonistic to the female, as we now know that one and the same gonad can produce both male and female sex hormones.

Finally, as Dr. Pratt has well stressed, the sociologic factor must be the guiding one in the management of these cases and much less attention should be given to the sex of the gonad than to such considerations as the patient's psychology, and the sex in which she has been brought up. It would be a cruel and unjustifiable procedure to try to convert into the opposite sex an individual who has lived as a female for many years, merely because she happened to have a male type of gonad.

DR. PRATT (closing).—The first patient had no vagina, and the urethra opened directly at the junction of the penis and perineum. There was not even a cloaca. By endoscopic examination the vas could be seen emptying into the urethra. After operation a little fluid could still be obtained by masturbation, but spermatozoa were no longer present in the fluid

THE PATHOGENICITY AND PHYSIOLOGY OF A PURE CULTURE OF TRICHOMONAS VAGINALIS*

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(From the Department of Obstetrics and Gynecology, State University of Iowa)

FOR eighty years after Donne[1] first described the human vaginal trichomonad in 1836, little attention was given to its possible pathogenicity. Hoehne,[2] in 1916, apparently developed the concept that the protozoon is a pathogen and introduced the term "trichomonaskolpitis" to express this relationship. During the succeeding years, opinion has been strongly divided as to whether the organism actually is responsible for the irritation with which it is associated or whether it is merely living symbiotically with bacteria that produce the inflammation. Previous investigators have shown that "trichomonas vaginitis" can be induced in an uninfected woman by inoculation with the vaginal discharge from one who is infected or with a mixed culture of the trichomonads and associated bacteria on artificial media. Other investigators (Hibbert and Falls)[3] have produced vaginal irritation and discharge by inoculations with the so-called *Streptococcus subacidus,* which they claim is frequently present in the "trichomonas vaginitis" discharge, and therefore took the position that the trichomonas is not pathogenic. It has, however, been well recognized that the controversy could not be settled until a pure culture of the protozoa was available for experimental inoculations.

Over the past four years, several workers in our laboratory have conducted innumerable experiments designed to develop a bacteria-free culture of the trichomonads but without success. In June, 1939, shortly after the start of a two months' concentrated effort in this direction, one of the stock cultures overgrew its associated bacteria and thus purified itself. We have no knowledge of the peculiar conditions which produced this result and consequently have been unable to repeat the purification on other strains. The original pure strain has been maintained for the past year on a liver infusion-human serum medium, transfers being necessary every fourth day. Rigid bacteriologic tests by three separate investigators have failed to reveal any evidence of bacterial growth. The media and methods employed will be presented in an appendix.

This strain of trichomonads, originally cultured from a case of human vaginitis, has been tested for human and animal pathogenicity, and certain experiments have been conducted to determine its physiologic behavior. A preliminary report[4] on the pathogenicity of the pure strain for human beings has already appeared. The present com-

*Read at the Sixty-Fifth Annual meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

munication reviews in detail the experimental, human, vaginal inoculations, summarizes the results of attempts to infect various animals, and presents the physiologic data now available. This last phase of the work will be continued.

HUMAN PATHOGENICITY

One nonpregnant and 28 pregnant women were subjected to experimental inoculations of the vagina with varying amounts of the pure culture of trichomonads. From 200,000 to 2,000,000 organisms were introduced, but a variable amount of the inoculum escaped promptly from the vagina. In a few instances, the culture employed for inoculation was relatively old in that active multiplication had ceased. The inoculation, which was carried out through a sterile speculum with the patient in the lithotomy position, was preceded by determination of the pH of the vaginal discharge, using the glass electrode technique,[5] by smears and hanging drop preparations, and by cultures for gonococci, monilia, and trichomonads. The smears were stained by the Hucker modification of the Gram technique, and the vaginal flora was classified according to Schroeder (Grade I, Döderlein bacilli only; Grade II, Döderlein bacilli plus other bacteria; and Grade III, no Döderlein bacilli). Cultures were made as follows: Gonococci, on chocolate agar according to Carpenter's[6] technique; "monilia" on Sabouraud's agar; and trichomonads, on placenta agar slants covered with Locke's solution plus 5 per cent human serum.[7]

None of the women used for the experiment presented trichomonads before the inoculation; gonococci were also uniformly absent, but in four instances "monilia" were recovered. The vaginal discharge was classified as Group I in 21, Group II in 7, and Group III in 1 case. The pH ranged from 3.9 to 5.4, and averaged 4.4.

The inoculated women were re-examined periodically for clinical evidence of vaginitis, and repeated culture and hanging drop examinations were made. When successful implantation of the protozoa became apparent, the discharge was studied bacteriologically for the presence of hemolytic streptococci, staphylococci, and colon bacilli.

Twenty of the pregnant women were refractory to attempted implantation of the trichomonads and did not develop any vaginal irritation. This fact argues

TABLE I. TWENTY WOMEN IN LATE PREGNANCY IN WHOM TRICHOMONADS COULD NOT BE IMPLANTED EXPERIMENTALLY*

CASE	AGE	VAGINAL pH	SMEARS	FOLLOW-UP EXAMINATIONS	
				NUMBER	DAY
1	29	4.12	I	2	6-9
2	25	4.59	I	3	4-6-8
3	26	4.13	II	3	4-6-8
4	23		II	4	2-4-6-18
5	21	4.13	II	1	12
6	25	4.32	I	2	3-14
7	23		I	5	2-4-5-6-9
8	22	4.58	I	4	3-5-7-19
9	25	4.39	I	3	3-5-7
10	28	4.30	I	3	3-5-7
11	18	4.41	I	4	2-5-7-9
12	28	4.52	I	4	2-5-7-9
13	24	4.83	II	3	3-5-7
14	27		I	6	2-4-6-9-23-25
15	26	4.42	I	5	3-5-10-12-24
16	27	4.29	I	2	2-7
17	35	3.99	I	2	4-7
18	36	4.23	II	2	2-19
19	23	5.41	III	2	3-5
20	40	3.98	I	2	5-7

*All examinations were negative for trichomonads and no cases of vaginitis developed.

against the possibility that a filtrable virus may be involved in the production of the vaginitis in those who were susceptible to inoculation with the protozoa.

Considering the known frequency of trichomonas vaginitis in all groups of women, consideration should be given to the possibility that some of the 20 women in this group were relatively immune to the protozoa because of a previous, natural infection. No data on this possibility are available. Small inoculums and old cultures may also account for some of the failures.

The remaining 9 women (1 nonpregnant and 8 in the last month of pregnancy) were successfully infected with the trichomonads. Preinoculation and follow-up findings are indicated in Table II.

Two of these patients presented no visible vaginal changes, in spite of the fact that the organisms were detected for twenty and twelve days, respectively.

In the third successful case, the protozoa were recovered ten days after the inoculation but had disappeared eight days later. There was slight reddening of the vaginal mucosa and a moderate purulent discharge, but no subjective complaints. The mucosal hyperemia persisted for a few days after the trichomonads had disappeared.

The fourth patient developed a mucopurulent, slightly frothy discharge by the tenth day, when the vaginal walls showed moderate diffuse reddening, and speculum introduction caused considerable discomfort. Two days later, the inflammation had subsided and the discharge was scant and white, in spite of the fact that the protozoa could still be demonstrated.

The fifth patient developed a vaginitis of slowly increasing severity; by the eighteenth day the vaginal walls were of a diffuse dark red color, and there was a moderate, watery, purulent, frothy discharge with some discomfort.

In the sixth successful case, the patient complained of chafing on the fourth day following the inoculation, when she showed moderate inflammation of the inner vulva and introitus, associated with a yellowish, bubbly discharge, which contained abundant trichomonads. Inflammatory changes in the vaginal mucosa were minimal. The changes persisted for several days, when the experiment was interrupted by delivery.

The nonpregnant patient (Case 7) complained of introital and vaginal soreness a few days after the inoculation. There was a scant, purulent, frothy discharge, and slight reddening of the introitus, which persisted with some variation in severity until the twenty-eighth day, when there was burning on urination, itching, soreness, and an increased watery discharge, and the vaginal mucosa became diffusely reddened. Menstruation began on the thirtieth day and lasted through the thirty-fourth day, with persistence of the urinary symptoms and vulval soreness. Two days after cessation of the menses, there was a definite exacerbation of all the signs and symptoms; the introitus was considerably inflamed; the vaginal mucosa was diffusely hyperemic; there was a moderate, watery, bubbly, purulent discharge; and introduction of a small speculum caused severe pain. One week later, after some spontaneous improvement, treatment was instituted.

The eighth patient revealed inflammatory reddening of the introitus and vaginal mucosa seven days after inoculation. There was a moderate purulent discharge, associated with vulval burning and itching, and increasing introital tenderness. The symptoms and local irritation persisted until she was delivered, nineteen days after introduction of the protozoa.

The ninth woman developed a yellowish, frothy discharge, containing many trichomonads, on the sixth day following inoculation. She was not seen again until ten days later, when there was a complaint of increased vaginal discharge and introital chafing for the preceding week. The vagina contained a copious, watery, bubbly, purulent discharge, which was slightly blood tinged, and the mucous membrane showed numerous ecchymotic patches upon a deeply reddened base. On bed rest, the local condition improved temporarily, but later became aggravated, and persisted until delivery, three weeks after the inoculation. On the ninth post-partum day, there were no complaints and no visible inflammatory reaction, although the trichomonads could still be demonstrated.

TABLE II. NINE WOMEN FROM WHOM TRICHOMONADS WERE RECOVERED AFTER EXPERIMENTAL INOCULATION

CASE	AGE	pH	SMEAR	FOLLOW-UP EXAMINATIONS			SYMPTOMS	SIGNS
				NO.	DAY			
					NEGATIVE	POSITIVE		
1	21	4.62	I	4	2-4-6	20	None	Vaginal discharge and mucosa remained normal.
2	21	5.12	II	3	5	7-12	None	Scant purulent discharge
3	19	4.10	I	6	3-7-18-28	5-10	None	Purulent discharge; slight mucosal reddening persisting after disappearance of protozoa.
4	23	4.59	I	5	3	5-7 10-12	Soreness	Mucopurulent bubbly discharge; diffuse moderate mucosal redness subsiding to normal by twelfth day.
5	30	3.96	I	3	4	7-18	Soreness	Purulent bubbly discharge; vaginal mucosa diffuse dark red. Duration 3 weeks.
6	24	4.04	I	4		4-7-8-9	Chafing	Purulent bubbly discharge; vulva and introitus inflamed.
7 Non-pregnant	19		II	9		5-10-13 16-23-28 30-36-42	Soreness Itching Burning on urination	Early purulent bubbly discharge; slight redness at introitus; vagina normal 4 weeks; on twenty-eighth day mucosa bright red; increased discharge; menses thirtieth to thirty-fifth day; thirty-sixth day exacerbation of symptoms and signs; some improvement forty-second day.
8	21	4.07	I	6	5	7-9-12 14-19	Soreness Itching Burning	Purulent discharge; increasing inflammatory reaction in vagina seventh to fourteenth days; slight improvement by nineteenth day.
9	18	4.31	I	7	2-4	6-17-18 25-30	Persistent chafing	Purulent bubbly copious discharge, slightly blood tinged; patchy mucosal reddening; duration 21 days (delivered); vagina normal on thirtieth day.

During the height of the local reaction following inoculation, smears from five of the nine successful cases showed no essential change in the vaginal flora, except that the leucocytic elements were increased. Moreover, cultures for hemolytic streptococci, staphylococci, and colon bacilli were negative in the 6 of the 9 patients from whom cultures were made.

COMMENT

The nine successful inoculations, with the development of the clinical picture of trichomonas vaginitis in 5 women of the group, indicate that the local irritation and discharge are due to the protozoa. The possibility of successful implantation apparently does not depend upon the type or acidity of the prevailing discharge, but rather upon such factors as the quantity of the inoculum, the virulence of the protozoa, and the susceptibility of the host. Failure to identify the *"Streptococcus subacidus"** in the successful cases indicates that these organisms are not essential to the development of vaginal irritation. At the same time, these results should not be interpreted to mean that the altered bacterial flora commonly associated with the protozoa in clinical trichomonas vaginitis does not influence the extent of the reaction, for such organisms might logically be assumed to aggravate the inflammatory process. Furthermore, it is reasonable to assume that certain vaginitides are of bacterial origin, with the protozoan parasites of secondary importance.

The discharge which developed in the successfully inoculated women presented the frothy character so frequently viewed as pathognomonic. It may be significant that pure cultures produce considerable gas from the carbohydrate of the culture media employed. Conceivably the frothiness of the discharge can be attributed to the reaction of the protozoa upon the carbohydrate available in the vaginal discharge, although the possibility of bacterial action cannot be eliminated.

ANIMAL PATHOGENICITY

With the cooperation of Dr. S. H. McNutt, of the Veterinary Research Institute, Iowa State College, an extensive series of animal inoculations has been made, using the pure culture of *Trichomonas vaginalis* here described, and the Glaser-Coria[8] pure culture of *T. foetus,* the bovine vaginal protozoon. These experiments will be reported in detail elsewhere, but are summarized here because they offer some evidence to refute the contention that the lower animals may be a source of human infection.

The pure culture of *T. vaginalis* could not be implanted successfully in the vaginas of cattle, sheep, swine, goats, horses, guinea pigs, rabbits, cats, or dogs; but could be maintained in *Macacus rhesus* monkeys, even though no irritation resulted. Oral inoculations in chickens, turkeys, and pigeons were unsuccessful, while rectal instillations in chickens and turkeys gave negative results. Guinea pigs, mice, and turkeys were inoculated intraperitoneally, and cattle, dogs, and rabbits were given intravenous injections of the pure culture without any apparent results.

*A culture of this organism has been available for study through the kindness of the Eli Lilly Company.

Intracranial inoculations in guinea pigs and rabbits were ineffective. Attempts to grow the organisms in developing chick embryos gave irregularly positive results, but it was found impossible to effect a prolonged series of transfers to other embryos.

Trichomonas foetus was successfully inoculated into cattle and temporarily into certain of the dog vaginas, but the remaining animals would not support the protozoa. Human inoculations with this species were not made, but it may be significant that several attempts to infect the vaginas of *Macacus rhesus* monkeys were unsuccessful, even though it was relatively easy to establish the *T. vaginalis* in this environment. The *T. foetus* was grown easily in chick embryos; this confirms Nelson's[9] report.

In addition to the obvious differences in the behavior of the two strains on animal inoculation, there are definite morphologic and cultural differences which argue strongly against any possibility of transmutation even under environmental changes. *Trichomonas foetus* has only three anterior flagella, while *Trichomonas vaginalis* has four. Moreover, there are essential differences in temperature resistance and media requirements which are well recognized and constitute important protozoologic criteria.

PHYSIOLOGY

A study of the physiologic behavior of *T. vaginalis* is now under way in cooperation with Garth Johnson of the Department of Zoology.

The data already collected have established an optimum growth range of pH 5.6 to 5.9 and have demonstrated that the greatest number of living organisms as determined by hemocytometer counts is present on the fourth day. At this optimum growth range, the average size of the protozoa as determined by A. Kupferberg is smaller than under less favorable pH conditions. Assuming that the size of the cells depends largely upon the rate of division the two observations correlate closely. On the other hand, deviation in either direction from the optimum pH results in decreased growth until division practically ceases at about pH 7.7 and 4.8.

The addition of dextrose markedly stimulates growth and increases the production of gas. Although the organisms grow well under "aerobic" conditions, anaerobiosis favors increased multiplication.

It may be significant that these observations on the growth of a pure culture in vitro correlate with conditions in the human vagina in cases of natural infection. The vaginal secretion in the majority of cases of trichomonas vaginitis is in the neighborhood of pH 5.5 to 6.0. The human inoculations here recorded indicate that a vaginal acidity well below pH 5.5 will not prevent the implantation of the protozoa, but it may be that the lessened acidity in natural infections is the result of the outpouring of alkaline fluid and cellular inflammatory products. This shift in pH creates in turn an even more favorable environment for the further development of the trichomonads.

The vaginal discharge is known to contain glycogen and its decomposition products, a situation which should encourage the growth of

the protozoa in view of the growth-stimulating action of dextrose in the pure cultures.

A third factor which probably favors the development of the trichomonads is that conditions within the vagina approach the anaerobic, especially in the fornices.

CONCLUSION

Trichomonas vaginalis can produce abnormal discharge and vaginal irritation in women irrespective of the associated bacterial flora or the degree of acidity present.

APPENDIX A

The medium used for maintenance of the pure culture of trichomonads consists of liver infusion agar slants (Difco) (autoclaved) covered with 5 per cent human serum in Ringer's solution (sterilized by filtration). The Ringer's solution contains NaCl 0.6 per cent, KCl 0.01 per cent, $CaCl_2$ 0.01 per cent, and $NaHCO_3$ 0.01 per cent. Heavier growth is favored by adjustment of the reaction to about pH 5.8 and also by the addition of 0.2 per cent dextrose. Transfers of 0.2 c.c. are made with pipettes every three to four days from the sediment at the bottom of the tube.

APPENDIX B

Cultures for bacterial sterility of the trichomonas have been made by us as follows: One drop of the trichomonas suspension on or in each of the following media in duplicate blood agar plates, endo agar plates, 5 per cent human serum in Locke's solution over placenta agar slants, meat infusion agar slants, plain agar slants, dextrin serum water, dextrose serum water, Russel's agar slants, dextrose meat infusion broth, bile peptone broth, chocolate agar slants, hormone agar, gelatin, blood agar slants, brain broth, and Sabouraud's agar. One set was incubated aerobically and the other anaerobically in a McIntosh and Fildes anaerobic apparatus, at 37°C. for eleven days. No bacterial growth could be demonstrated.

The culture of *T. vaginalis* was also submitted to the Department of Bacteriology, which reported as follows: Six tubes each of dextrose meat infusion broth, dextrose meat infusion blood broth, dextrose meat infusion agar, blood agar, chocolate agar, hormone agar, ascitic fluid agar and Sabouraud's agar were inoculated with one drop of the trichomonas culture. Two tubes of each set were then incubated fourteen days at 37°C. under aerobic, anaerobic and 20 per cent carbon dioxide conditions.

"Only one tube (dextrose meat infusion agar slant) had any growth after the two weeks' incubation period. This one tube showed evidence of contamination twenty-four hours after inoculation, and the growth was undoubtedly a contaminant from some outside source.

"These results indicate that the trichomonas culture is apparently free from bacterial contamination."

APPENDIX C

The techniques employed for detection of gonococci, "monilia," and trichomonas in these experiments have been used in this department for several years[5, 10] with considerable success. The cultural diagnosis of trichomonas has yielded slightly more positive results than has the examination of the fresh vaginal discharge. In this study, however, both methods were employed in the majority of the examinations.

APPRECIATION.—We wish to acknowledge the kindness of Mr. Pelczar and Dr. Porter (Department of Bacteriology) who tested the trichomonas cultures for contamination. Sincere appreciation is extended to Dr. Theo. Jahn (Department of Zoology) for his generous cooperation and to Dr. R. C. Miller for his assistance in the earlier phases of the human pathogenicity experiments.

REFERENCES

(1) *Donne, A.:* Compt. rend. Acad. d. sc. **3:** 385, 1836. (2) *Hoehne, O.:* Zentralbl. f. Gynäk. **40:** 4, 1916. (3) *Hibbert, G. F., and Falls, F. H.:* Am. J. Obst. & Gynec. **36:** 219, 1938. (4) *Trussell, R. E.:* J. Iowa M. Soc. **30:** 66, 1940. (5) *Trussell, R. E., and MacDougal, R. F.:* Am. J. Obst. & Gynec. **39:** 77, 1940. (6) *Carpenter, C. M.:* Recommended Methods for the Laboratory Diagnosis of Gonococcal Infections, Am. Pub. Health Assn. Year Book, pp. 125-134, March, 1937. (7) *Stein, I. F., and Cope, E. J.:* Am. J. Obst. & Gynec. **22:** 368, 1931. (8) *Glaser, R. W., and Coria, N. A.:* Am. J. Hyg. **22:** 221, 1935. (9) *Nelson, P. M.:* Proc. Soc. Exper. Biol. & Med. **39:** 258, 1938. (10) *Tucker, W. W., Trussell, R. E., and Plass, E. D.:* Am. J. Obst. & Gynec. **38:** 1055, 1939.

DISCUSSION

DR. GRANDISON D. ROYSTON, St. Louis, Mo.—Dr. Plass suggests the possibility that some of the 20 women in whom trichomonads could not be experimentally implanted may have acquired a relative immunity. Our clinical experience on the other hand seems to show that previous infection confers no such immunity.

Presumably pregnant women were largely used for this experiment because of their greater local resistance to infection. With the statement that the optimum growth range of the organisms is a pH 5.6 to 5.9, I fully agree, and with the statement that a vaginal pH well below 5.5 will not prevent the implantation of the organisms I also agree. It is known that perhaps 5 per cent of trichomonads will not respond to a pH control, but these particular trichomonads are nearly always in a state of symbiosis with some other organism or organisms. In this presentation, there were seven instances in which no associated organisms could be demonstrated.

Roblee of the Washington University Clinic feels that maintaining the acid base balance over a period of two to four weeks determines the ability or inability of trichomonads to persist in the vagina. This maintenance of acid base balance is a normal result of endocrine influence, and the pH balance determines the organisms present. A pH favorable for cure is maintained by inserting into the vagina a No. 11 veterinarian capsule with 80 per cent anhydrous beta lactose, and 20 per cent boric acid, often enough to favor the growth of the Doederlein bacilli. Usually one capsule inserted at bedtime is ordered when treatment is begun, and the intervals lengthened as the discharge diminishes, but repeated often enough to keep some of the powder constantly present in the vagina until a cure is effected.

I should like to ask Dr. Plass two questions: First, have the organisms in his study been cultured successfully for two or more weeks in a pH 4 to 4.5? Second, have the implants persisted in the vagina with the environment controlled to a pH 4 to 4.5 over a period of two weeks' time?

DR. PLASS (closing).—The use of pregnant women in this series was determined entirely by their availability, since we have a large ante-partum group. We also naturally have given thought to the possibility of endocrine influences, and I inferred that when I mentioned environment.

Dr. Royston's questions about the maintenance of a reduced pH on the organisms in the vagina can be answered only partially. We believe that decrease of the pH to 4.0 would certainly prevent the multiplication of the organisms, either in the vagina or in test tubes. We have not, however, followed the changes in pH in the vaginas of these infected women.

The experimental work has been done largely by Mr. Ray Trussell, a third-year medical student.

ROENTGEN PELVIMETRY AS A ROUTINE PRENATAL PROCEDURE*

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DURING the past six years a roentgenometric survey of the pelvis has been performed on every primigravid woman who has presented herself prenatally for delivery in the wards of the New Haven Hospital. The results have amply proved the value of the procedure and the recent prediction by J. M. M. Kerr that such investigation will eventually become an essential part of prenatal care seems definitely justified.

Many methods for a roentgen survey of the pelvis have been devised. Some of these are not only complicated and require expensive equipment but considerable experience is required in order to secure satisfactory results. It seems obvious that any method which may become usefully adaptable in such a universal field as that of obstetrics must be of reasonable simplicity, of ready interpretation, and of low expense. Such a method is that used in our clinic and one which has been developed through an experience of nearly a score of years. This method employs two films, depicting two views of the pelvis: an inlet view and a lateral view. It is my conviction that for routine purposes the information secured from these two films together with that obtained by certain manual methods offers an excellent survey of the bony pelvis for routine obstetric purposes. Such a survey embraces the measurement of certain pelvic diameters and the evaluation of certain pelvic contours. In order that these important diameters may be easily comprehended we may divide the pelvis into three portions. These are:

1. The plane of the pelvic inlet
2. The midpelvic plane
3. The planes of the pelvic outlet

A knowledge of the contours and of certain diameters of these planes gives not only a concept of the architecture of a given pelvis but will furnish an excellent index as to the available space present in the bony birth canal. I have described these planes and their diameters as follows:[1]

The Plane of the Pelvic Inlet.—(See Figs. 1 and 2.) From the obstetric point of view, this plane is bounded anteriorly by the posterior upper surface of the symphysis pubis and the forward portions of the

*Description of a moving picture film presented at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Quebec, Canada, June 17 to 19, 1940.

iliopectineal lines, laterally by the iliopectineal lines, and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. It should be noted that this plane is not that of the anatomic superior strait, but rests slightly below this. The useful diameters of this plane are: (1) anteroposterior, (2) transverse, and (3) posterior sagittal.

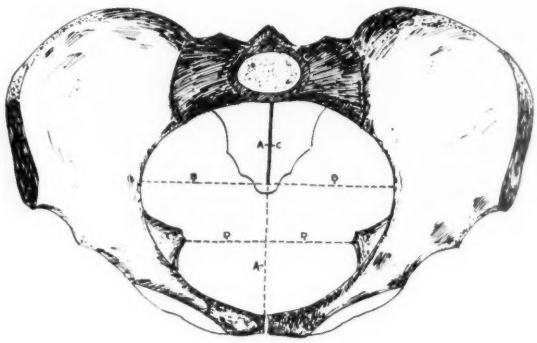


Fig. 1.—The plane of the pelvic inlet. *A*, anteroposterior diameter; *B*, transverse diameter; *C*, posterior sagittal diameter; *D*, transverse of midplane, see text. (From Am. J. Roentgenol. **44**: 9, 1940.)

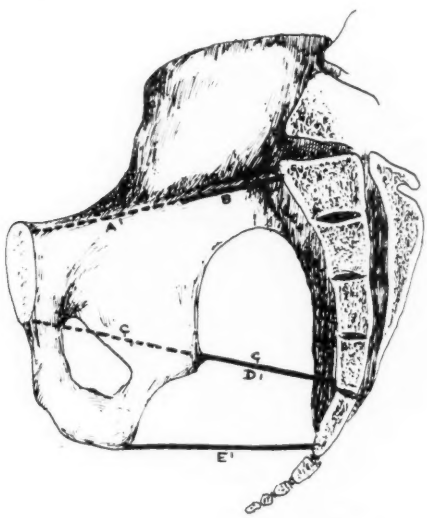


Fig. 2.—Anteroposterior pelvic diameters seen in lateral aspect. *A*, anteroposterior diameter of inlet; *B*, posterior sagittal diameter of inlet; *C*, anteroposterior diameter of midplane; *D*, posterior sagittal diameter of midplane; *E*, posterior sagittal diameter of outlet. (From Am. J. Roentgenol. **44**: 9, 1940.)

1. The *anteroposterior diameter* of the pelvic inlet extends from a point on the upper posterior surface of the symphysis about 1 cm. from the superior border, posteriorly to the anterior surface of the first sacral vertebra at the point where the iliopectineal lines would meet if they were to be continued. (This point of convergence may or may not be located at the sacral promontory. It is usually somewhat below this eminence.)

2. The *transverse diameter* of this plane is the widest transverse distance separating the iliopectineal lines. It bisects the anteroposterior somewhat posterior to its midpoint, dependent upon the shape of the plane of the pelvic inlet.

3. The *posterior sagittal diameter* of the inlet is represented by that portion of the anteroposterior diameter which lies posterior to the point of intersection by the transverse diameter. The length of this diameter is an index of the amount of space in the important upper posterior pelvis and when abnormally shortened usually represents a posterior displacement of the transverse diameter. This displacement may accompany an abnormal convergence of the iliopectineal lines anteriorly, or, in the case of the flat pelvis, be due to a definite anteroposterior shortening of the pelvic inlet. If due to the latter, the discrepancy between the lengths of the anteroposterior and transverse diameters is at once apparent.

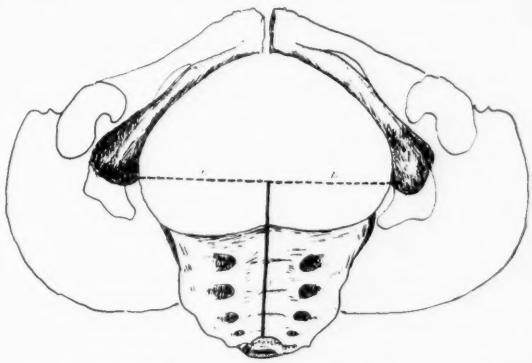


Fig. 3.—The important outlet diameters seen from below. *A*, transverse diameter; *B*, posterior sagittal diameter. (From Am. J. Roentgenol. 44: 9, 1940.)

The Midpelvic Plane.—(See Fig. 2.) The second obstetric plane is the midpelvic plane. It is somewhat ovoid in form, large anteriorly and small posteriorly, being narrowed posteriorly by the convergence of the sacrosciatic ligaments. This plane has been defined as being bounded anteriorly by the lower border of the symphysis pubis, laterally by the ischial spines, and posteriorly by the tip of the sacrum. However, these points are not truly in the same plane, for the tip of the sacrum is usually as much as 2 cm. below the level of a line joining the lower border of the symphysis with the bispinous diameter. Therefore, the posterior limit should be placed in the lower third of the sacrum and will usually find itself at the junction of the fourth and fifth sacral segments.

The three diameters which are of obstetric significance in this plane are the transverse or bispinous, the anteroposterior, and the posterior sagittal. This latter diameter, as in the case with the plane of the pelvic inlet, represents that distance on the anteroposterior diameter which lies posterior to the point of intersection by the transverse or bispinous diameter.

Planes of the Outlet.—(See Fig. 3.) The third portion of the pelvis of definite obstetric significance is the pelvic outlet. This is in reality two planes, represented by two triangles, the bases of which join each other along the line of the bituberal diameter. The anterior triangle is bounded by the bones forming the pubic arch, the shape of which is of considerable obstetric significance. The two diameters of particular significance are the transverse of the outlet or bituberal diameter, and the posterior sagittal. This latter diameter extends from a midpoint on the bituberal diameter posteriorly to the tip of the sacrum.

In addition to the above diameters, which are of great usefulness in determining pelvic capacity, we should mention certain pelvic contours which are also of importance. The shape of the pelvic inlet, the vertical and lateral contours of the anterior sacral surface, the shape of the sacrosciatic notch, the convergence of the pelvic side walls and the prominence of the ischial spines, and the character of the pubic arch are all considerations which should be taken into account.

To recapitulate, we can say that the significant diameters for use in the routine survey of the bony pelvis are:

Pelvic inlet	Anteroposterior Transverse Posterior sagittal
Midpelvic plane	Anteroposterior Transverse or bispinous Posterior sagittal
Pelvic outlet	Transverse or bituberal Posterior sagittal

The above measurements may be considered the cardinal diameters of the pelvis. All of the above data including the findings of manual examination may be conveniently summarized on the pelvic estimation chart shown in Fig. 4 which is filed with the patient's prenatal record.

PELVIC VARIATIONS

Variations in form of the bony structures of the pelvis show wide distribution. From the studies of W. W. Greulich and myself[2] it would appear that the description of the normal female pelvis as noted in most modern textbooks requires considerable revision. Our studies have shown that in white women in this country that type which has been previously described as normal based upon the shape of the pelvic inlet probably occurs in less than one-third of women. In order to study pelvic variations it is necessary to make a simple classification into which certain groups may fall. If such a measure is based upon the general shape of the pelvic inlet and the relation of its two principal diameters to each other, a good working classification becomes available. Attempts by other observers to classify pelves according to sex characters are bound to be confusing, as the intermingling of sex characters is so great that clinical adaptation of such classification becomes of considerable complexity. Moreover, our studies of pelves in male adults

have shown us that in male pelves, also, great variation is found.[3] Furthermore, the use of a simple dimensional means as a basis for classification eliminates the disadvantages bound to arise from information based largely on subjective impressions.

We consider, therefore, that in general the pelvic inlet may assume one of four shapes, which may be described as: (1) an anteroposterior oval; (2) a circle; (3) a transverse oval; and (4) an exaggerated trans-

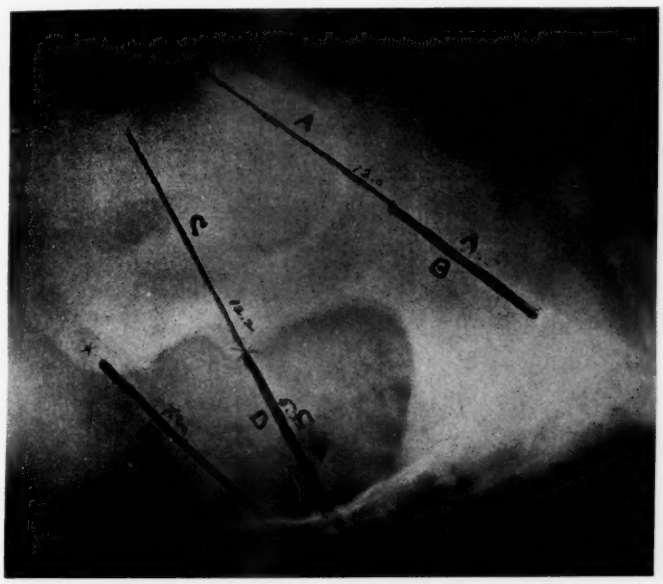


Fig. 4.—Film of lateral pelvis. Lines indicate cardinal diameters. *A*, anteroposterior diameter of inlet. *B*, posterior sagittal diameter of inlet. *C*, anteroposterior diameter of midplane. *D*, posterior sagittal diameter of midplane. *E*, posterior sagittal diameter of outlet. (From Am. J. Surg. 39: 56, 1940.)

verse oval. We can further describe this morphology by considering the relation of the anteroposterior and transverse diameters of these figures to each other, and on this basis we may adopt terms for pelvic types which will be useful:

1. Dolichopellic or anthropoid type pelvis. The transverse is less than the anteroposterior diameter.

2. Mesatipellic or round type pelvis. The transverse is equal to, or slightly greater (not more than 1 cm.) than, the anteroposterior diameter.

3. Brachypellic or oval type pelvis. The transverse diameter is more than 1 and less than 3 cm. greater than the anteroposterior diameter.

4. Platypellic or flat type pelvis. The transverse diameter is 3 cm. or more greater than the anteroposterior diameter.

The above classification is useful simply as a basis for description of individual pelves. It is obvious in the individual case that the obstetrician is not so much concerned with the group in which a pelvis may align itself as he is with the measurements and contours which reveal its useful capacity for childbearing. Given the eight cardinal

diameters which have been described, together with a consideration of the important contours, such as inlet, notch and pubic arch, one can form a fairly adequate estimation of pelvic capacity for obstetric purposes.

It is important to know the chief characteristics of male pelves which which may affect female pelves.

1. The male characteristics which may affect the pelvic inlet are: (a) The inlet is in general more circular. (b) The widest transverse diameter is, therefore, slightly displaced posteriorly. (c) The posterior sagittal diameter is, therefore, relatively shortened.

2. The male characteristics which may affect the midplane are: (a) The narrowing of the pelvic side walls with increase in size and prominence of ischial spines results in a relatively decreased bispinous diameter. (b) Laterally the male type or narrow sacrosciatic notch decreases posterior pelvic capacity in this plane and is manifest in a relatively shortened posterior sagittal diameter.

3. The male characteristics which may affect the pelvic outlet are: (a) Narrowing of the pubic arch with less arcuate formation of its sides and relative shortening of the bituberal diameter. (b) Because of the forward displacement of the sacrum forming the posterior wall of the male notch, the posterior pelvic capacity in this plane is also decreased, which is manifest in a relatively shortened posterior sagittal diameter of the outlet.

Male characters may appear in female pelves at the inlet, the midpelvis, or the outlet, and in a certain small group of pelves they may occur in all three portions, the complete male pelvic type. It is obvious that they may have a considerable obstetric significance, particularly in the latter instance.

Some idea of the distribution of these basic pelvic types in white women of the clinic group may be gained from their incidence in 800 primigravidae who were delivered at term (child 2500 Gm. or over) in the New Haven Hospital (Table I).

Again the fact impresses us that 62 per cent of this series present pelves whose inlet is not that described as normal in textbooks of

TABLE I

TYPE	NUMBER	PER CENT
Dolichopellic	129	16.12
Mesatipellic	367	45.88
Brachypellic	272	34.00
Platypellic	32	4.00

TABLE II

TYPE	100 NURSES	582 CLINIC WOMEN	107 CHILDREN
Dolichopellic	37.0	14.5	57.9
Mesatipellic	46.0	44.5	33.6
Brachypellic	17.0	34.3	8.3
Platypellic	----	6.7	

anatomy. In a recent study by Greulich and Thoms of the pelvic inlets in 789 white females, which included 582 clinic women, 100 nurses, and 107 young females from 5 to 15 years, the incidence of pelvic types was

as indicated in Table II. The incidence of the various types in the student nurses seems especially significant in view of the superior physical status and economic level of the women comprising that group. The data from the younger girls are also of significant interest, showing the high incidence of the dolichopellic type in this group.

ROENTGEN TECHNIQUE FOR PELVIMETRY

The following technique is essentially that described by H. M. Wilson and myself in 1939[4] and again by myself in 1940.[1]

For routine purposes we take two views: One of the pelvic inlet by the so-called grid method, and one lateral projection. It has become obvious to us that an adequate survey of the pelvis for obstetric purposes is not possible without the employment of both techniques. Furthermore, inasmuch as the mensuration of the anteroposterior diameter of the pelvic inlet may be determined in both views, each procedure becomes an excellent check on the accuracy of the other. Our routine is to take the lateral projection first, and this technique may be described as follows:

1. The patient removes her clothing, putting on heelless slippers and the usual hospital bed gown open at the back.

2. She is placed standing in front of an erect Bucky diaphragm or an adjustable cassette changer, such as is used for chest work, with either the right or left lateral aspect of the body toward the target. The arms are folded across the chest.

3. The target film distance is 36 inches and the target is centered at a point on the external conjugate diameter one-third the distance from the symphysis pubis to the depression under the fifth lumbar vertebra.

4. A binder is placed around the patient and attached to the cassette changer to insure further steadiness during the exposure.

5. Before the exposure is made, an upright metal rod (lead and iron) with a centimeter scale perforated in a lead strip is placed posterior to the patient close to the fold of the nates.

6. The time of exposure varies with the thickness of the patient, all other factors being constant; in general the time is from seven to twelve seconds.

Comment on Lateral Technique.—When developed and viewed the following landmarks should be readily identified (Fig. 4): anterior and posterior borders of the symphysis pubis, acetabula, ischial spines, ischial tuberosities, the lower lumbar vertebrae, the promontory and anterior surface of the sacrum, and the sacrosciatic notch. On one edge of the film may be seen the shadows cast by the perforations giving corrected centimeters in the sagittal plane of the patient. By means of calipers, using this scale, any diameters in this plane may be measured.

The advantages of this lateral technique may be summarized as follows:

1. All the anteroposterior diameters of the bony pelvis may be measured, including those of the pelvic inlet, midpelvis, and inferior strait. The anterior and pelvic inlet diameters of the important midpelvic plane are readily determined.

2. The contours of the anterior surface of the sacrum may be studied, a matter of importance in the recognition of sacral abnormalities, especially those due to the influence of rickets.

3. When lateral roentgenograms are made at term or in labor, the relation of the presenting part to the superior strait may be studied with advantage.

The centimeter grid method for pelvic inlet pelvimetry may be described in its essentials as follows:

1. The patient is placed on the roentgenographic table in a semirecumbent position which is maintained by a backrest. In placing the patient in position we endeavor to make the pelvic inlet of the pelvis horizontal.

2. The level of the pelvic inlet above the sensitive film is established as follows: (a) By means of calipers the vertical distance is measured from some point on the table top to a point on the anterior surface of the symphysis pubis 1 cm. below its superior border, or this point in space may also be determined by measuring downward with a tape from some point on the tube stand. (b) By means of calipers the distance is determined from the interspinous space between the fourth and fifth lumbar vertebrae, as determined by palpation, and the table top. For practical purposes, an imaginary line drawn between the posterior point on the body and the point on the upper and anterior surface of the symphysis will bisect the plane of the pelvic inlet.

3. The tube is centered in the midline about 6 cm. posterior to the upper border of the symphysis and the exposure is made.

4. The patient is removed from the table, the tube and exposed film remaining in situ.

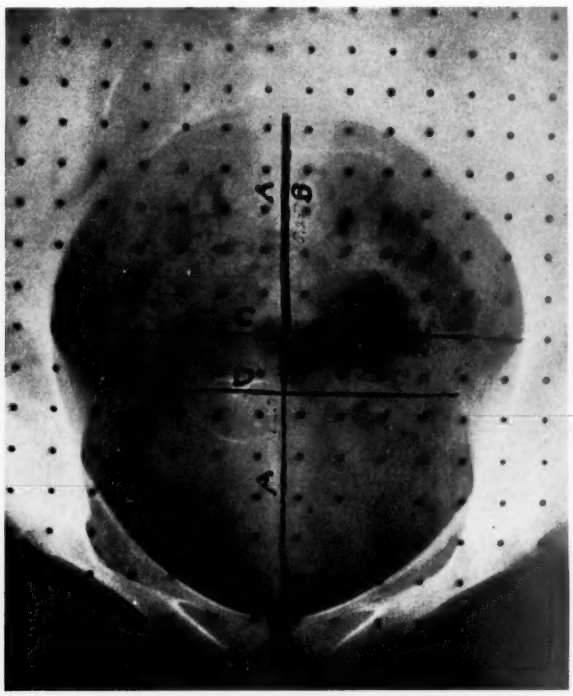


Fig. 5.—Film of pelvic inlet. Lines indicate cardinal diameters. *A*, anteroposterior diameter of inlet. *B*, posterior sagittal diameter of inlet. *C*, transverse diameter of inlet. *D*, transverse diameter of midplane. (From Am. J. Surg. 39: 56, 1940.)

5. The centimeter grid, a lead plate with perforations exactly 1 cm. apart, is introduced into the same plane as that previously occupied by the pelvic inlet, as determined by the caliper readings and the measuring tape, and a second (flash) exposure made on the previously exposed film.

In viewing the film an outline of the pelvic inlet is shown (Fig. 5) and any diameters of this plane may be measured, using the dots as a centimeter scale. The interspinous diameter may also be measured in this film, using a correction table for the level at which they rest in the pelvis. This level is determined in the lateral film.

In a recent communication[5] I have described a simple calibrated calipers for measuring pelvic diameters, thus eliminating the use of the

grid and the upright rod. The general principle, however, remains the same and identical results can be secured by both techniques.

It will be noted that in addition to the important pelvic contours the two films make available seven of the eight cardinal diameters. The intertuberal or transverse diameter of the outlet may be adequately estimated by the usual manual method, thus saving the exposure of an additional film.

With this additional knowledge of pelvic dimensions and pelvic architecture, it is obvious that a great deal of experience must be gained before the proper clinical evaluation may be secured. In a previous communication[5] I have made such a study based upon the results in 200 primigravidas. This, however, is but a beginning of a study which must be further expanded. One thing seems apparent, that no longer need we be ignorant of the important dimensions of the bony pelvis in any given case, and this knowledge combined with skillful clinical experience will make for better obstetrics.

In conclusion, we must be reminded again that the knowledge of pelvic dimensions and contours is but one part of a complex obstetric picture which must be viewed as a whole for successful prognostication and the skillful conduct of delivery.

The conclusions in this paper were derived from investigations aided by grants from the Clinical Research and Teaching Funds of Yale University School of Medicine.

REFERENCES

(1) *Thoms, H.:* Am. J. Surg. **3:** 691, 1940. (2) *Greulich, W. W., Thoms, H., and Twaddle, R. C.:* J. A. M. A. **112:** 485, 1939. (3) *Thoms, H., and Greulich, W. W.:* Am. J. Obst. & Gynec. **39:** 56, 1940. (4) *Thoms, H., and Wilson, H. M.:* Yale J. Biol. & Med. **11:** 179, 1939. (5) *Thoms, H.:* Am. J. Roentgenol. **44:** 9, 1940.

DISCUSSION

DR. HOWARD C. MOLOY, New York, N. Y. (By Invitation).—Dr. Thoms in his classification recognizes three anatomic forms: the long oval, the round, and the transverse oval. He also recognizes an overlapping of these types. This classification was proposed by Turner in 1885. A fourth group has been added (brachypellic) which may be said to represent an intermediate type between the round form on the one hand, and the transverse oval on the other. In addition to these types, the presence of masculine characteristics must be considered. It is to be observed that two controversial aspects of the question of morphologic classification present themselves. The first deals with the use of three or four classic shapes to illustrate the blending from the longitudinal oval through the round to the transverse oval type. Anthropologists consider that these variations in shape represent normal growth variants and believe that the intermediate types are so numerous that a classification cannot be sufficiently simplified to consist of three or four groups. In our roentgenologic studies we have also been impressed with the frequent occurrence of types which are not exactly a longitudinal oval form, nor are they round in shape. We believe, therefore, that some provision should be made for the classification of these mixed forms. (Fig. 1.)

The second controversial point deals with the so-called masculine type of pelvis. Dr. Thoms provides for this type by advising that masculine characters at the inlet, the midpelvis, and the outlet may be described for each pelvis in addition to the classification as determined by the ratio between the inlet measurements. But extreme masculine forms occur which, in our opinion, should be included as definite types in a formal classification. These two important points must be

settled before a standard classification can be accepted. In the future, the worker interested in the study of pelvic morphology must deal with the classification of pelvic shapes which are borderline between the long oval, the round, or the transverse oval. He must attempt to determine the significance of masculine characters.

In recent years considerable emphasis has been placed upon measurements as obtained by methods of roentgen pelvimetry. Unfortunately a roentgen technique devised for pelvimetry purposes may fail to permit visualization of the pelvis

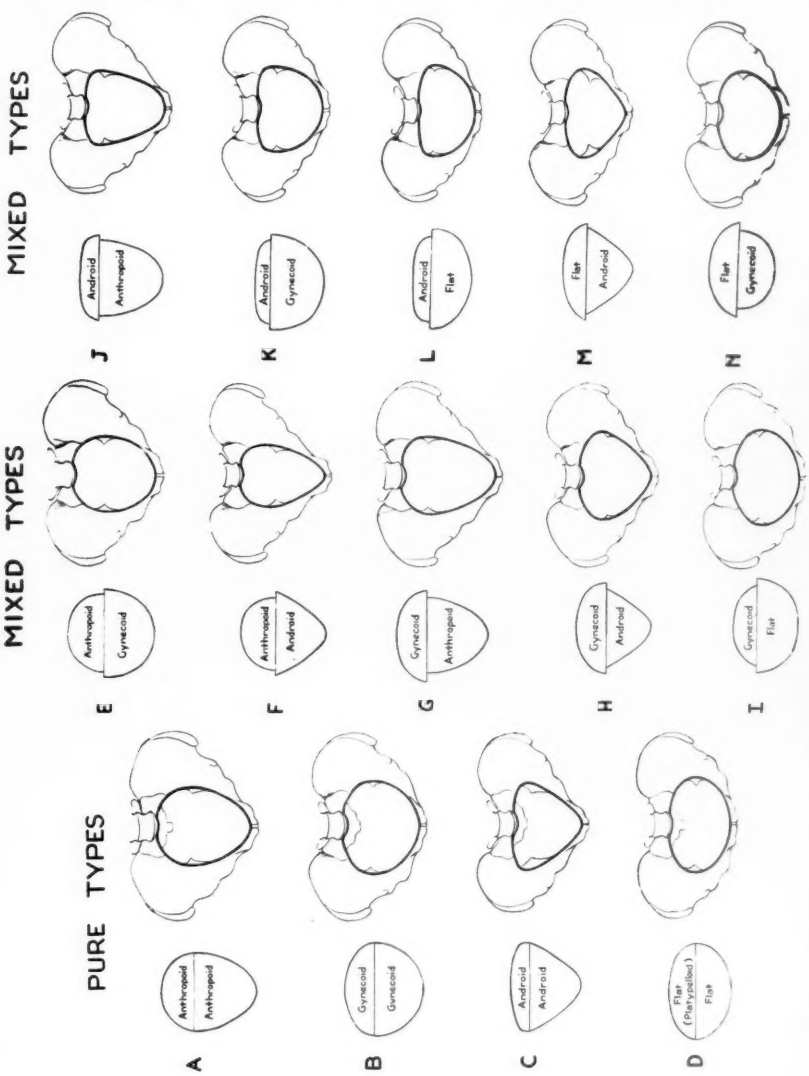


Fig. 1.—The four pure forms present a characteristic inlet shape to the anterior and posterior segments. Mixed types are classified on the principle of the combination of the posterior segment of one pure form with the anterior segment of another. Fourteen types occur; four pure and eight mixed. Anthropoid-flat and flat-anthropoid forms represent impossible theoretical types.

from inlet to outlet. In the use of the flat film technique, the worker should appreciate the possible sources of error in measurement and the effect of distortion upon pelvic shape if errors in technique occur.

Our experience with the method described by Dr. Thoms has been limited. But from experiments on skeletal pelves, we have found that accurate measurement of the widest transverse diameter of the inlet is dependent upon placing the grid in the plane of the inlet. This correct plane at the widest transverse diameter is usually 2 to 3 cm. below a line joining the promontory and the superior posterior

aspect of the symphysis. If by chance the grid is placed above this precise inlet plane, an error in the measurement of the widest transverse diameter may occur. (Figs. 2 and 3.)

We must realize that with flat films, distortion of the inlet shape occurs when the plane of the inlet is tilted, thereby giving an imperfect inlet view. In Fig. 4 a true inlet view to the left and a slightly sloping view to the right are shown. In the slightly sloping view to the right, the angle of the forepelvis is elevated above the film to a greater degree than regions in the posterior pelvis. As a result the forepelvis is wider and the posterior pelvis is flatter than exists in a more perfect inlet view. By experimentation we have found that the difference in tilt between cases comparable to the two shown in this slide represents approximately twenty degrees. The magnitude of the distortion present in the example to the right, Fig. 4, *B*, in our opinion, should preclude tracing of this inlet for use as an index of its shape. For this reason we believe stereoroentgenograms are more satisfactory than flat films in the interpretation of pelvic morphology and the fetal pelvic relationship.

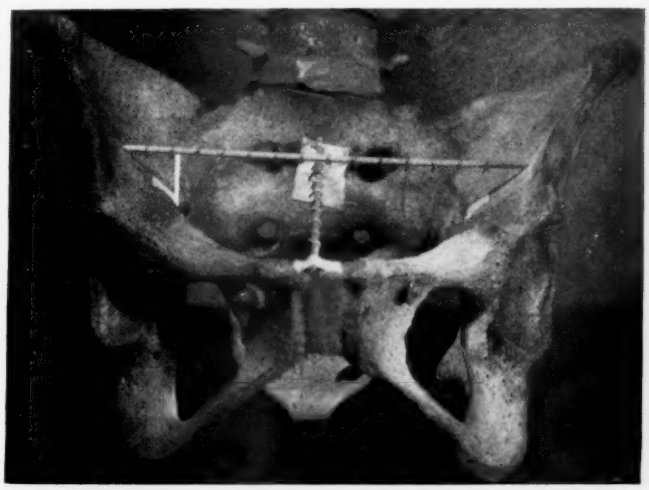
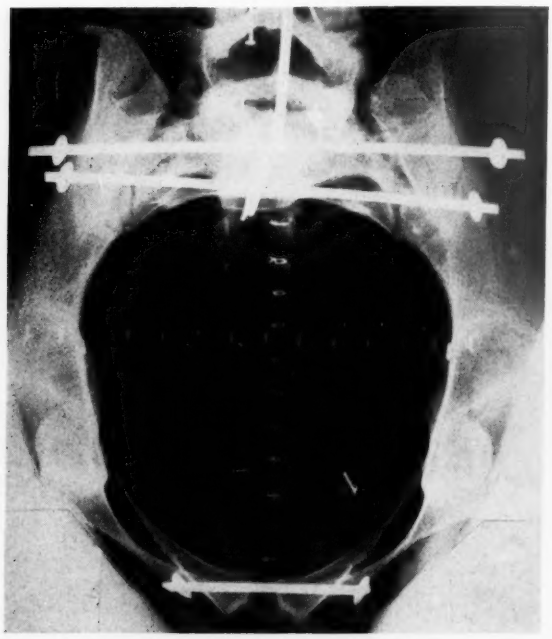


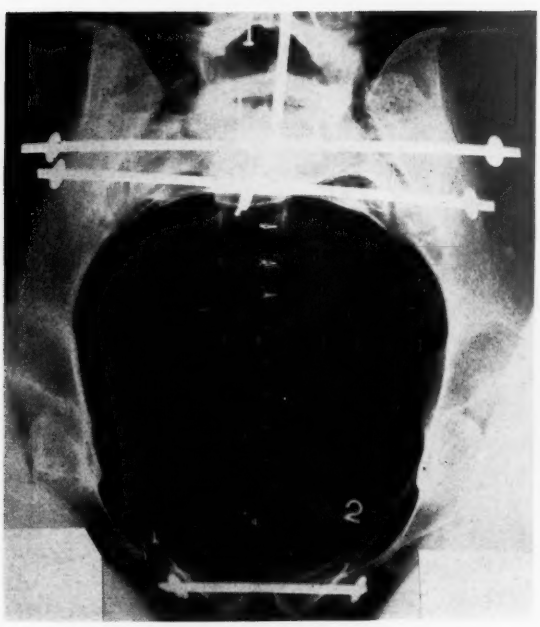
Fig. 2.—When the plane of the grid is situated on a line joining the symphysis and promontory, the grid is considerably above the plane of the widest transverse diameter of the inlet. This causes more distortion in the grid than exists at the plane of the inlet, and an error in the widest transverse diameter occurs (see also Fig. 3).

The lateral roentgenogram supplies a method of measurement of the true conjugate diameter and at the same time gives information regarding the inclination and curvature of the sacrum. The most significant anatomic observations to be made from the lateral roentgenograms are those relating to the posterior pelvis, especially in regard to relationship of the lower sacrum to the ischial spines. The manner in which a forward sacrum may decrease pelvic capacity behind and below the ischial spines can be seen at a glance without complicated methods of analysis. A simple method which we have found very useful is shown in Fig. 5, *A*. Observe the length of the posterior sagittal diameter behind the spines and the parallel relationship to the plane of the inlet, the same plane previously referred to in the placement of the grid for accurate measurement of the widest transverse diameter. The forward encroachment of the sacral tip and the level of the sacrococcygeal platform to the ischial spine are clearly evident.

Hodges, Ball, Snow, and others have offered their own method for analysis of the lateral roentgenogram. These workers have used one common principle. This refers to lines drawn from the top of the symphysis at a tangent downward and backward to the sacral tip and to the lower sacral region through the ischial spines.



A.



B.

Fig. 3.—*A*, In this skeletal pelvis, the grid was placed between the symphysis and the promontory considerably above the plane of the widest transverse diameter. As a result, the grid records greater distortion than actually exists at the plane of the inlet. Roentgen measurement of widest transverse diameter is 10.8 cm. Actual skeletal measurement of the same diameter is 11.4 cm. Error is 0.6 cm. *B*, When the grid is placed in the true plane of the inlet, an accurate roentgen measurement results. The grid cannot be placed with precision in the correct inlet plane in the living patient in all instances.

The anteroposterior diameter of the midplane as defined by Thoms slopes downward and backward from the under surface of the symphysis to the junction between the fourth and fifth sacral segments. Fig. 5, *A* shows that the length of these lines, especially when drawn from the top of the symphysis to the sacral tip, is not at all significant inasmuch as the head, in the mechanism of labor, has

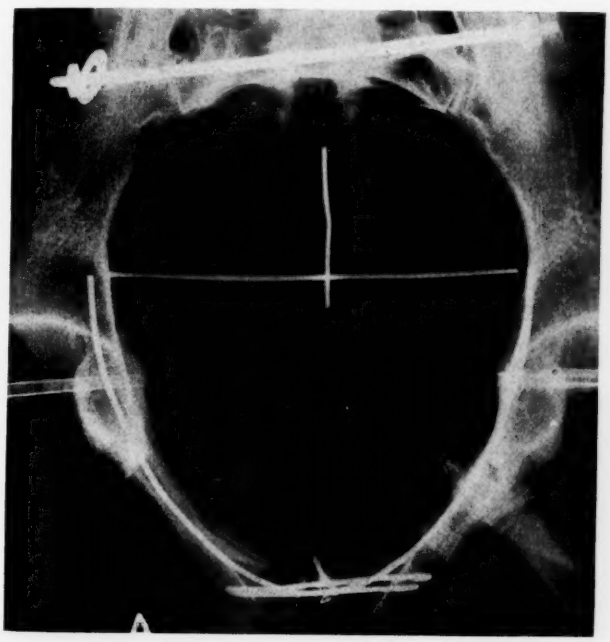


Fig. 4, *A*.

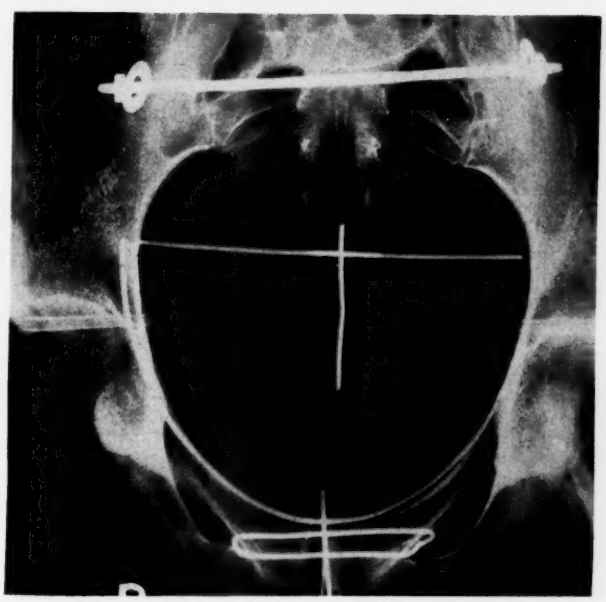
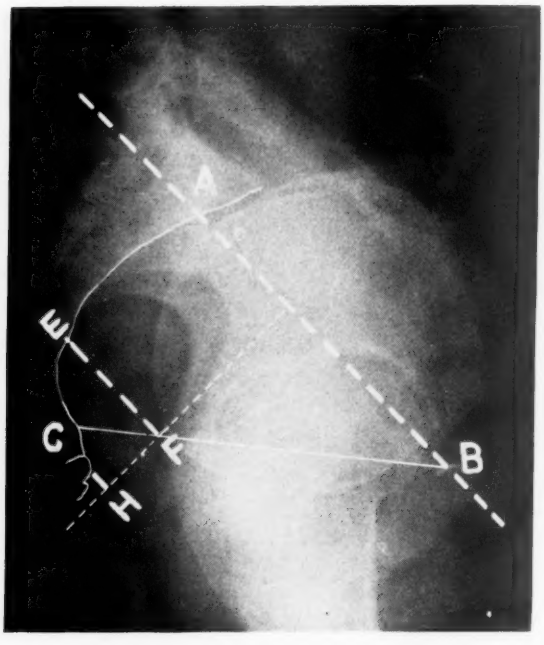


Fig. 4, *B*.



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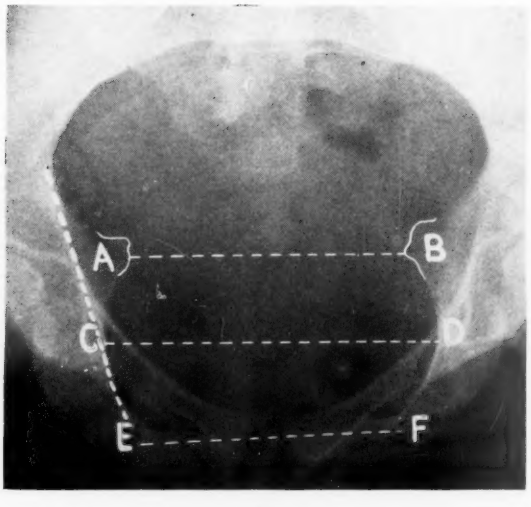

B.

Fig. 5.—*A*, Lateral analysis: *AB*, plane of inlet. *BC*, Tangent line from top of symphysis to lower sacral region. *EF*, Posterior sagittal at level of ischial spines. *FH*, Level of sacrococcygeal platform to the ischial spines.

B, The intertuberous diameter is more correctly considered as the widest transverse diameter of the outlet *CD*. The convergence of the side walls toward the lower aspects of the pubic rami does not denote the origin of the widest transverse diameter of the outlet, but rather a line which passes transversely across a small segment of the outlet *EF*. The interspinous diameter *AB* is always smaller than the widest transverse diameter of the outlet.

long since passed below the symphysis before the obstruction offered by the lower sacral region is encountered. Therefore, from the obstetric standpoint, the length of the posterior sagittal at the level of the spines, and its level with respect to the sacral tip, shows at once the degree of encroachment of the sacrum on the lower pelvis. Available outlet space is determined by the length of diameters extending parallel from points on the lower pubic rami to the lower sacrum rather than by lines from the top of the symphysis to the lower sacrum.

Finally, somewhat similar remarks may be made in reference to the intertuberous diameter. Dr. Thoms advises clinical methods for measurement. Ball and Snow in recent publications have chosen a point where the line of the side walls intersects the lower pubic rami as the intertuberous diameter. As shown in Fig. 5, *B*, this diameter as described by them is actually shorter than the interspinous diameter in many instances, and this gives an erroneous index of the width of the outlet. The intertuberous diameter from the roentgenologic and clinical standpoint has not been defined with accuracy, because it is difficult to pick out the significant anatomic point of origin of this important diameter. As the pelvic view shown in Fig. 5, *B* indicates, the significant transverse diameter at the outlet is the "widest" diameter in the lower forepelvis. This diameter does not originate from any specific location on the tuberosities of the ischium, because this widest diameter varies with the character of the base of the ischial spines behind and in front with the inward curvature of the pubic rami. This diameter may be termed the "widest transverse diameter of the outlet."

I regret that time does not permit a detailed description of the various observations made in arriving at the conclusions mentioned in this discussion. The pioneer work of Dr. Thoms in roentgen pelvimetry has been appreciated by our specialty for many years.

A SIMPLE METHOD OF MAKING AN ARTIFICIAL VAGINA*

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THE operative creation of a normal vagina is impossible. The creation of an epithelial-lined tube which may be used for normal cohabitation is not only possible, but is a relatively simple procedure. Its successful accomplishment depends on a knowledge of anatomy and some experience in gynecologic plastic surgery. One of the great difficulties in developing an adequate technique for the performance of this operation is the lack of suitable clinical material on which to base technical experience. Many operators of considerable gynecologic experience have seen only one or two cases. Therefore it follows that no one operator has had sufficient personal experience with the various operations proposed to be able to express an opinion regarding their comparative merits and disadvantages.

The indication for the operation may be open to some difference of opinion. Primarily it should be undertaken purely as a means of providing for cohabitation in women presenting this defect who are married or contemplate matrimony. It would also seem reasonable to defer operation in all cases until the patient was about to be married so that the act of coitus would preserve the patency of the artificially prepared tube. Dannreuther[1] has suggested that estrin should be present in the blood, that the patient should be young and attractive and have a normal sex urge. There is another factor which should be kept in mind which we feel is more important in some cases than in others. There is a natural inferiority complex in some of these patients, because of the knowledge of the abnormality; and this may be greatly lessened if an attempt is made to form an artificial vagina, even if the attempt is not entirely satisfactory from an anatomic standpoint, and even though they fail to menstruate subsequently.

The embryologic development of the vagina is not entirely clear and accepted by various authorities in this field. Koff[2] has summarized the various views, and we believe that the one that best fits the clinical findings in patients presenting absence or deformity of the vagina is as follows:

The lower one-third of the vaginal tube develops from the sinovaginal bulbs (urogenital sinus) and the upper two-thirds from the caudal portion of the uterovaginal canal (Müllerian ducts). Clinically we see some patients who have a total absence of the upper two-thirds of the vagina and still present a shallow pouch which represents the rudimentary lower one-third. Other patients present an entire absence of the vaginal tube. Apparently the upper two-thirds never develops independently of the lower one-third. It is an important fact that in a large

*Read, by invitation, at the Sixty-Fifth Annual Meeting of the American Gynecological Society, The Seigniory Club, Que., June 17 to 19, 1940.

proportion of these women the uterus, tubes, and ovaries are very rudimentary or may be absent in whole or in part.

The first attempt to create an artificial vagina which we were able to find was by Dupuytren,[3] in 1817, which consisted of making an opening between the rectum and vagina and inserting tampons to maintain patency while epithelization was occurring. This method was not very successful.

Mackenrodt,[4] in 1911, formed a similar tunnel and transplanted vaginal mucous membrane from another patient. The result of this procedure was unsatisfactory.

Baldwin,[5] in 1907, excised a ten-inch loop of ileum and united the ends of the remaining bowel by end-to-end anastomosis. He then tunneled between the bladder and rectum and pulled the middle of the excised loop downward; and after opening it, he sewed the edges to the skin of the perineum. This left a mucous membrane-lined cavity which did not shrink and whose walls were smooth and nonirritating. The obvious objection was the danger involved, and that following ingestion of food an irritating secretion from the vagina was noted in some of these cases.

Schubert,[6] in 1911, described a method involving the use of the bowel which depends on freeing the lower six inches of the rectum, transposing it forward to a new opening on the perineum where the vulval opening should be, and drawing down the upper end of the bowel to the anal opening. This implies the removal of a considerable portion of the coccyx to expose the rectum, and there is considerable danger of infection following operation, and damage to the function of the sphincter ani.

In 1927, Frank and Geist[7] made a tubular graft from the inner surface of the thigh with a base near the vulva. Three weeks later this was freed at its distal end, opened, and sutured over a rubber plug with the epithelial surface next to the plug. By blunt dissection a cavity was created between the bladder and rectum, and into this the plug with its epithelial covering was fitted, bringing the subcutaneous fat surface of the graft into approximation with the raw surface of the canal. The rubber plug was removed in eight days and in two weeks the graft was healed in place.

Graves[8] has suggested the creation of a blind pouch by blunt dissection between the bladder and rectum and the formation of a lining for the same by using epithelial strips cut from the labia minora and the sides of the vulva, and sewed over a glass model bringing their free edges together. The model is removed and the pouch is then inverted into the cavity, and held in place by a glass cylinder until attachment is established.

Wharton[9] describes a technique similar to that by Meigs in which he used a condom filled with paraffin as the vaginal plug after creation of a space between bladder and rectum by blunt dissection. He reports four successful cases by this method. He stresses the importance of the proliferatory power of the vaginal epithelium in lining the cavity thus created and feels that the operation might not be successful in cases where there was no evidence of beginning vaginal formation before operation.

Masson[10] has been the chief sponsor of the Baldwin operation in this country, having published five cases in 1932 without a death and with good functional results.

Judin[11] reported six cases without mortality, using the Baldwin technique, and is an enthusiastic advocate of the procedure. He admits however a mortality of 10 per cent in a group of cases done in Russia by surgeons who reported their results to him personally, and a mortality rate of 14.1 per cent in a series of 105 cases collected by Rabinovitch.[12] He points out also that in a series of 61 cases of the Popov-Schubert operation a mortality of 4, or 6.6 per cent, is reported.

Emil Novak[13] in a personal communication reported five cases done by the Baldwin method without mortality.

Meigs,[14] in 1938, described a procedure that seems very simple if practical. He tunneled between the vagina and rectum, inserted a pyrex glass tube and held it in place with a "T" binder, later doing a skin graft to bring the skin of the vulva up to the epithelium-lined pouch thus formed. He reported only one case which was successful, although there was difficulty in keeping the tube in place and preventing infection.

Counsellor[15] and Babcock[16] working independently have used Thiersch's grafts cut from the inner thigh and sewed around a glass tube with the skin side next to the tube. A tunnel was made sufficiently deep between the bladder and rectum and the tube introduced and held in place for a week. The canal was kept open by passing a well-lubricated glass tube daily.

In the opinion of most observers, including the writer, the methods using the bowel, either ileum or rectum, are potentially too dangerous in the hands of the average gynecologic surgeon and have other objections that render them not the first choice for a given case.

The Frank-Geist operation necessitates prolonged hospitalization (ten weeks) which may be an insurmountable financial barrier to some patients.

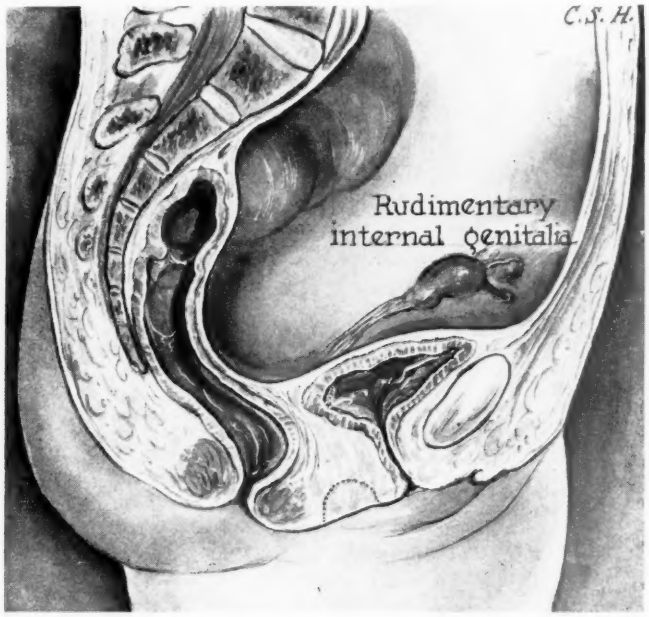

Fig. 1.—Anatomy of congenital vaginal defects.

The Graves method is open to two main objections: First, that hair growth may occur on the inverted flaps; Second, if sloughing occurs, the operation cannot be easily repeated. There is also undesirable distortion and mutilation of the vulva.

OPERATIVE TECHNIQUE

The operation here described is extremely simple, devoid of dangers and gives satisfactory results in the cases in which it has been used. As a rule in these patients, the external genitalia are fairly well formed, and in many there is a slight pouch or at least a dimple in the perineum to indicate the normal location of the vagina. A circular incision is made around the edges of this dimple, creating a disk about 2 to 3 cm. in diameter. The edges of this disk are undercut, leaving the center attached to the underlying tissue. The loose connective tissue between the bladder and rectum is separated by blunt dissection, and the disk of skin is pushed inward to form the vault of the new vagina. Skin flaps about 1 cm. wide

are cut from the edges of the vulval opening by making lateral cuts at 3 and 9 o'clock, the width of the flap, and extending the incision upward and downward for about 2 to 3 cm., making two ribbons attached to the side of the vulva at one end which can be swung into the cavity, and the free edge sewed to the edges of the disk, forming the vault of the new vagina. The same is done on the opposite side so that we have four strips of vulval mucosa 1 cm. wide, each attached externally to the edge of the vulva and internally sewed to the disk forming the vaginal vault

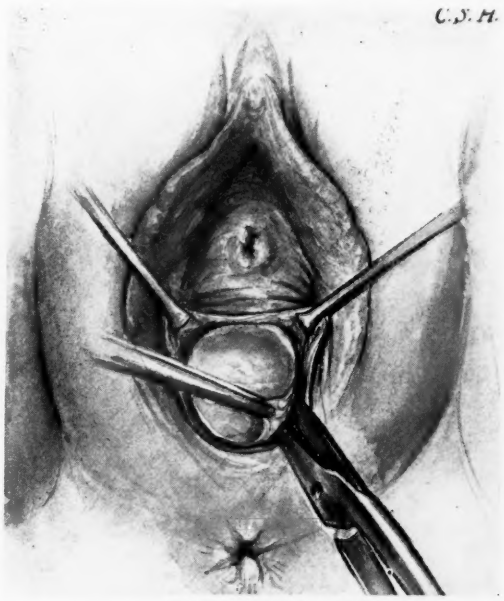

Fig. 2.—Dissection between bladder and rectum.

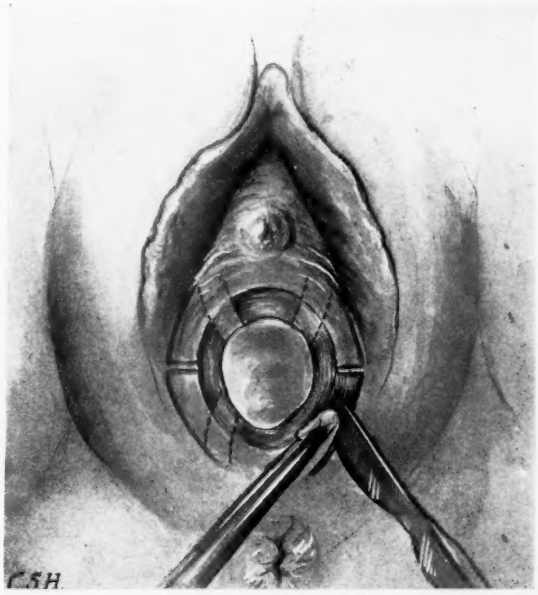

Fig. 3.—Dissection of flaps after freeing disk.

by catgut sutures. The raw surface of the flap comes in contact with the walls of the cavity formed to permit sinking the disk, and the blood supply is established between the two. The flaps also get a good blood supply through their attached pedicle. Epithelization occurs between these transplanted strips of mucosa, and in about two weeks a completely epithelized tube is formed. During healing, the pouch is packed with gauze daily, and a moderate amount of pressure is maintained.

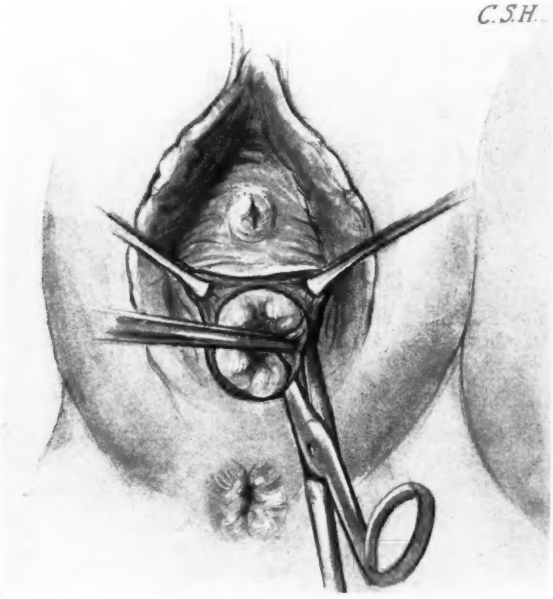

Fig. 4.—Freeing edges of vaginal pouch.

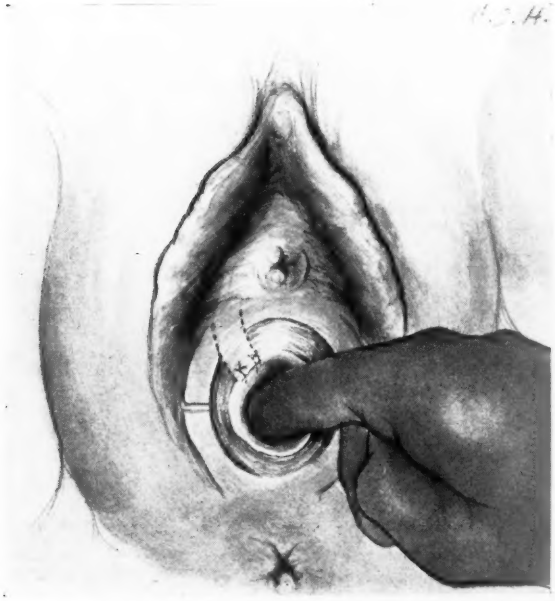

Fig. 5.—Sinking pouch and flap formation.

After healing is complete, the pouch will be found to be about two inches deep, and may be deepened by wearing a vaginal plug at night and making rather strong pressure on the disk or vaginal vault daily. The patient can be taught to do this herself.

In cases in which a rudimentary pouch is present to start with, or in cases in which a rudimentary vagina has been created by the above mentioned technique, the outer edges of the pouch are separated from the vulva and undercut deeply (two inches). The whole pouch is then pushed inward and flaps are again cut from the edges of the vulva, and turned in to meet the edges of the counter-sunk pouch.

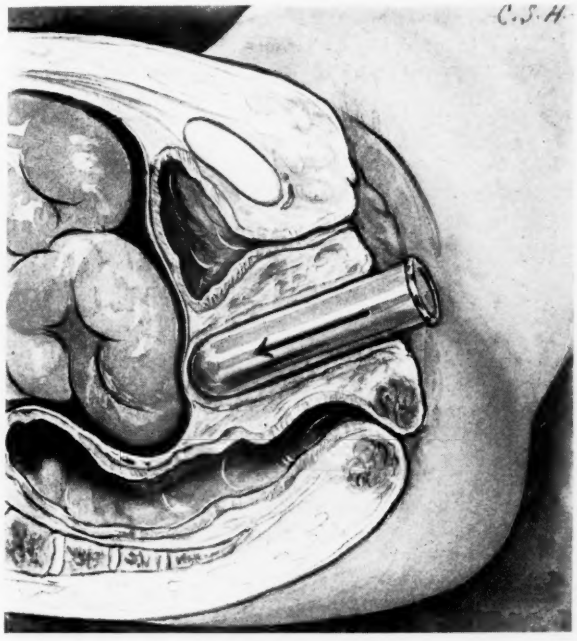

Fig. 6.—Glass or rubber tube used for distending and elongating pouch.

The cavity is packed as before. Epithelization again takes place between the flaps, and the pouch thus formed is five or six inches deep. Healing is usually complete in two weeks, after which further deepening of the pouch can be attained by daily stretching and by pushing inward with a vaginal plug. We have had no complaint of secondary contraction of the pouches nor of undue dryness of the epithelium. There is no hair growth on the strips turned in, so that there is no irritation on that score.

As in the case with most surgeons, my personal experience with the correction of this anomaly is limited to a few cases, some of which, however, have been sufficiently complicated to be of considerable interest.

CASE REPORTS

CASE 1.—In 1927, a 19-year-old white girl entered the Gynecological Service at the University of Iowa, complaining of cramplike pain in the lower abdomen recurring every month, but with no menstruation. She had had the symptoms off and on for two years. She was engaged to be married, had normal libido and had attempted intercourse on several occasions. On examination a pouch about one inch deep was found between the urethra and fourchette. Rectal examination revealed no mass or evidence of retained menstrual blood. I made a crucial incision in the vault of the rudimentary vaginal pouch and inserted a needle cautiously between

the bladder and rectum following with blunt dissection until on advancing the needle I aspirated urine and knew that I had penetrated the bladder. I then enlarged the tract so that it admitted the tips of two fingers, the whole pouch being about three inches deep. Thinking I might be able to connect with this pouch by downward dissection from above, I opened the abdomen and found no uterus, tubes, or ovaries in the normal position. I was about to close the abdomen when at the left inguinal ring I noticed a small uterus 1 cm. long by 0.5 cm. wide with a rudimentary left tube and ovary. I clamped the pedicle at the ring and removed the specimen. Postoperatively I packed the vaginal pouch and had the patient dilate it with a test tube daily. Epithelization occurred and a satisfactory vaginal tube four inches deep resulted.

CASE 2.—In 1926, a 27-year-old married colored woman entered the Cook County Hospital at Chicago, complaining of monthly cramps in the lower abdomen. The abdomen showed no tumor masses or tender areas. The vagina was absent. The external genitalia were fairly well developed. On rectal examination a mass about as large as a cervix could be felt at about the location of a normal cervix. I cut in between the rectum and bladder, making a tunnel about three inches deep, but could not reach the nodule. I therefore opened the abdomen suprapubically and found a rudimentary bicornuate uterus didelphus with a fibroid about 2 cm. in diameter on each cornu. A fibrous strand connected the lower end of these structures to the region between the rectum and bladder where the vagina should have been. The uterine corpora were about 3 cm. long. I had mistaken one of the fibroids for a cervix. I attempted to produce a vaginal pouch by packing the tunnel I had made with gauze. The patient left the hospital and could not be traced thereafter, so that the ultimate success of the operation is in doubt. An interesting fact in these cases is the "dysmenorrhea" which each of these patients complained of in spite of the fact that there was no evidence of blood retention and most rudimentary internal genitalia.

CASE 3.—On Jan. 18, 1934, a 25-year-old married white woman presented herself, who had at the age of eleven noted some vaginal bleeding one night, and never experienced this again. She complained of dysmenorrhea on a few occasions that might have corresponded to times she would have been menstruating. She came to the clinic because she wanted to become pregnant and had never menstruated. Physical examination revealed no marked anomaly except that the vagina was very shallow, 1½ to 2 inches long, and the uterus including the cervix and adnexa were not palpable. She was operated upon by the method here described and a normally appearing six-inch vaginal tube was produced.

CASE 4.—E. L., aged 27 years, office clerk, had congenital absence of vagina. She had consulted three physicians when 16 because of failure to menstruate. She was given pills but not examined. She paid no further attention to the condition until at the age of 21 she experienced abdominal cramps while at work. The company physician examined her, made the diagnosis and referred her to a specialist who recommended operation when she wanted it. She came to our out-patient department five years later when she contemplated marriage. Not even a rudimentary pouch was present. She was operated upon on Nov. 25, 1936, for the first step of our operation, and the second step on April 15, 1937. Following this operation a pouch five inches long which admitted two fingers snugly was created.

CASE 5.—A rather unusual patient presented herself at the Cook County Hospital in April, 1937. There was a rather shallow pouch about three inches deep which was partially prolapsed. The woman was a widow and had had sex relations for several years but had neither menstruated nor conceived. On examination, the vagina was represented by a blind pouch. The uterus could not be palpated and there were some tumor masses in the region of the ovaries. It was decided to attempt a suspension of the vaginal pouch. The abdomen was opened and a rudimentary uterus with atrophic tubes and ovaries was found. The masses previously mentioned proved to be multiple fibroids of the round ligaments up to 4 or 5 cm. in diameter. The vaginal vault was suspended as well as possible with the

remains of the round ligaments and the infundibulopelvic ligaments. The atrophic ovaries were left in situ. The results on leaving the hospital were good with the vault well suspended. On June 8, two months later, this patient returned with a complete prolapse of the vaginal pouch. I opened the abdomen in the midline, and freed a 5 cm. strip of rectus fascia 1 cm. wide from the lower angle of the wound on each side, leaving it attached at its pubic end. The pouch which was previously carefully prepared as for a total hysterectomy and packed with antiseptic gauze was pushed upward by an assistant with an eight-inch forceps from below. The vault was opened and the fascial strips were sewed into the angles of the pouch. The abdomen was closed around the strips. When seen several months later, the vaginal pouch was well supported, and there was no interference with bladder function.

CASE 6.—C. McR., white, American, aged 17 years, entered the hospital Feb. 16, 1939, stating she felt well and was unaware of the condition until seven months ago. For two months prior to coming to the hospital she had vicarious nasal menstruation, the last occurring on three successive nights and being scant. When 13 years of age on one occasion she had hemorrhages into the skin and from the mouth, which lasted only one day.

Examination revealed poorly developed breasts and scant pubic hair, normal external genitalia with a rudimentary vaginal pouch which admitted the tip of the fifth finger to a depth of 2 cm. Rectal examination revealed no uterus or right ovary, but a mass which was taken to be the left ovary in the left adnexal region. She was operated upon according to our technique with production of a four-inch pouch which contracted to three inches three months later. This illustrates the desirability of waiting until just before marriage in these cases before operating.

CASE 7.—M. V., white, American, aged 27 years, entered the hospital Feb. 13, 1939. At the age of 19 she was examined by a physician in Springfield, Illinois, because of a nervous breakdown, who told her she would have to have a "skin graft operation below" and referred her to a physician in St. Louis. Because of so much pain during the examination, she had to be anesthetized. On waking up she found that she could not retain her urine and has been incontinent ever since. At the age of 24 she became engaged to be married and had intercourse on several occasions. When 26 she consulted a physician regarding her incontinence and was for the first time told that she did not have a vagina. A combined abdominal and vaginal operation was done to cure the incontinence which resulted in failure before she left the hospital.

Examination revealed good general development; the breasts were small and poorly developed; the clitoris was hypertrophied and what appeared to be a normal vaginal orifice admitted two fingers easily. On inserting two fingers into this opening, however, there was a gush of urine, and it was evident that the pouch represented the dilated urethra. A medium-sized vaginal speculum could be readily passed, and on spreading the blades the interior of the bladder could be easily visualized. There was no evidence of a vaginal orifice, and no uterus could be palpated. Two masses in the adnexal regions were taken to be ovaries.

In this case two conditions presented themselves: It was necessary to perform an operation for incontinence caused by the tremendously dilated urethra and at the same time produce an artificial vagina. According to our technique of stretching the vaginal pouch after turning in the flaps, there was danger that any repair that might be made in the region of the vesical neck might be damaged by stretching. It was therefore thought advisable to attempt to produce the artificial vagina first and follow this by a plastic on the urethra. On February 22, and March 17, 1939, the first and second stages of our operation for an artificial vagina were performed. Following the second operation, there was moderate vaginal bleeding which necessitated repacking. On leaving the hospital, the vaginal pouch was about two inches deep. She returned April 18, 1939, for operation for incontinence. The vaginal pouch had contracted and was only about an inch and a half deep. The anterior wall of the pouch was incised and the dilated urethra and base of the bladder were plicated by two layers of No. 2 chromic catgut and the

third layer of silk sutures which narrowed the urethra until it admitted a catheter snugly. The vaginal pouch was again deepened. The patient left the hospital having good control of the urine. Control was maintained for three weeks when the patient stated she passed something through the urethra (probably silk stitches) and following this incontinence returned. She returned to the hospital on Aug. 8, 1939, at which time the urethra was found to be much smaller but the patient complained of incontinence on standing. A urethral sphincter was made by crossing the bulbocavernosus muscles underneath the urethra from each side. This resulted in good control, and the patient had a perfect result when she left the hospital as far as the incontinence was concerned. The vaginal pouch, however, was still only about two inches deep, but it was thought best not to attempt further dilatation of this until complete urinary continence could be established for some time, for fear of weakening the newly formed sphincter, keeping in mind that the urinary incontinence was the principal complaint of this patient when she presented herself at the clinic.

CASE 8.—About two years ago a 3-year-old child was brought to our pediatric out-patient clinic by its mother. Examination revealed a total absence of the vagina. The mother was advised to do nothing about the condition, but to explain the situation to the child when it reached the age of puberty and to have her seek gynecologic advice should she later contemplate matrimony. Since in our experience these patients are usually mismanaged when seen by general practitioners and general surgeons, written instructions to the mother are advisable which should be transferred to the child at the proper age.

DISCUSSION

Since there have been so many successful operations proposed for the correction of this anomaly, one hesitates to suggest a different procedure. I was stimulated to develop the method here described by the impression gained from the literature that most of the methods had at least some minor objections. The technique was evolved with an eye to meeting these objections in whole or in part, and producing a safe operation that could be done successfully by men possessing the average skill in gynecologic surgery.

The method here proposed is totally devoid of danger. It uses to the utmost any rudimentary vaginal canal and vaginal epithelium that may be present. It gives a partially epithelized sac to start with, namely, the vault and the strips that are turned in. These form epithelization centers from which new epithelial cells grow out rapidly to cover the intervening raw spaces. There are no hair follicles on the skin that is used to form the pouch, and of course none on the areas covered by the epithelial cells that grow out from and unite the strips previously turned in. There is no irritating discharge from the tube and no unusual dryness of the canal has been noted or complained of by the patient. The turned in flaps and central disk have shown no tendency to slough, and the epithelization of the tube has been rapid and complete. This is probably due in a large part to the double blood supply to the flaps, the light pressure maintained by the gauze pack and the maintained blood supply of the central disk.

It is true that the secondary deepening of the tract in some cases necessitates a second hospitalization, but since the first step only requires about a week in the hospital, the total stay does not exceed that for many operative procedures. The operation may be done very well under local anesthesia.

The results in these cases have been on the whole very satisfactory. There have been no general reactions or wound infections.

It is to be hoped that, for a time at least, gynecologists attempting repair in these conditions will report their findings and results, to the end that pooled experience may lead us to the most practical solution of this very interesting problem.

REFERENCES

(1) *Dannreuther, W. T.:* Am. J. Obst. & Gynec. **35:** 452, 1938. (2) *Koff, A. K.:* Curtis' Obstetrics and Gynecology, Philadelphia, 1933, W. B. Saunders Co., **1:** p. 577. (3) *Dupuytren:* Quoted by Judin, Surg. Gynec. Obst. **44:** 530, 1927. (4) *Mackenrodt:* Zentralbl. f. Gynäk. **35:** 1017, 1911. (5) *Baldwin, J. F.:* Am. J. Obst. **56:** 636, 1907. (6) *Schubert, F.:* Zentralbl. f. Gynäk. **35:** 1017, 1911. (7) *Frank, R. T., and Geist, S. H.:* Am. J. Obst. & Gynec. **14:** 712, 1927. (8) *Graves, W. P.:* Gynecology, ed. 1, Philadelphia, 1916, W. B. Saunders Co., p. 667. (9) *Wharton, L. R.:* Ann. Surg. **107:** 842, 1938. (10) *Masson, J. C.:* Am. J. Obst. & Gynec. **24:** 583, 1932. (11) *Judin, S.:* Surg. Gynec. Obst. **44:** 530, 1927. (12) *Rabinovitch:* Quoted by Judin, Surg. Gynec. Obst. **44:** 530, 1927. (13) *Novak, Emil:* Personal communication. (14) *Meigs, J. V.:* Am. J. Obst. & Gynec. **35:** 465, 1938. (15) *Counsellor, V. S.:* Ibid. **35:** 467, 1938. (16) *Babcock, W. G.:* Ibid. **35:** 468, 1938.

30 North Michigan Avenue

DISCUSSION

DR. JAMES C. MASSON, Rochester, Minn.—Dr. Falls' method of making an artificial vagina appeals to me as being simple and satisfactory but, as with all plastic procedures, it requires extreme patience and care in carrying out details, not only on the part of the surgeon but also on the part of the patient.

Until recently I have been an advocate of the Baldwin procedure. I felt that there was comparatively little risk to the operation and that the results were universally good. In my first ten cases the results were excellent and convalescences were absolutely normal for abdominal operations. Since then, I have performed the operation in four cases with two deaths, and I have now decided that the operation cannot be done safely in all cases. Both patients died from peritonitis as the result of sloughing of the isolated loop of ileum, owing to traction from a too-shortened mesentery. When the mesentery of the terminal portion of the ileum is long enough, the Baldwin operation is a comparatively easy procedure for any surgeon accustomed to intestinal work.

The advantages of the Baldwin operation are: (1) One operation, (2) short hospitalization, (3) no tendency toward contracture, and (4) a normal moist mucous surface. If the terminal portion of the ileum is used, there is no irritation of the skin from the discharge. There should be no danger of obstruction, either early or late, or of adhesions as the result of the anastomosis. The disadvantages are: (1) Unsuitable in some cases, (2) the risk connected with the operation, and (3) the undue amount of secretion. If not more than 10 inches (25.4 cm.) of ileum is used, the secretion is not a cause for worry or inconvenience to the patient and tends to decrease in amount.

Since 1936, at the Clinic we have used in 30 cases the McIndoe method or a modification of it, inlaying Thiersch grafts, and I am satisfied that this is a satisfactory and safe method. I think there are just three requisites to obtaining a good result by this method: (1) Meticulous care in obtaining a dry field to be grafted; (2) obtaining a one-piece, uniformly good thin skin graft; (3) use of an obturator for several weeks or until marriage. The results obtained by this method are so satisfactory that I doubt the advisability of performing the Baldwin operation except in special cases.

Perfect results are obtained with the McIndoe operation in about 50 per cent of cases. By a perfect result, I mean a complete take of the primary graft. In some cases secondary skin grafts or time for skin to grow over the total surface from isolated islands of skin and the long use of the obturator are required.

In three or four of the cases in which this method was used at the clinic complete traumatic destruction of the vagina has been present. The vaginal canal of one of these patients was reconstructed by Dr. Counseller and the uterus later was connected with it: this woman has been pregnant and about three weeks ago a cesarean section was performed on her by Dr. Counseller.

DR. NORMAN F. MILLER, Ann Arbor, Mich.—Being somewhat interested in mechanical devices, I felt I could improve upon the obturators used in these cases and built one in my own shop out of the modern plastics. I discovered that the plastic was a very undesirable thing to use, because the entire graft sloughed and the patient came near to developing a fistula. The plastic appeared to be corroded by the tissue. Since then we have used only glass.

The other point I wish to refer to is the administration of estrogenic substances. At present we are using large doses of estrogen which we hope will be of benefit in establishing the mucosa in these cases.

DR. EMIL NOVAK, Baltimore, Md.—In the early days I tried various sorts of plastic operations, using flaps from the vulva or thigh, and the results were disappointing, chiefly because of the tendency to contraction and shrinkage of the canal. My experience with the Baldwin operation has been far more satisfactory, and I still think that no other operation can give such a perfect imitation of the normal vaginal canal. On the other hand, it is very definitely a major operation, although my impression, based on the four cases in which I have carried it out, is that it should not be a difficult operation for anyone accustomed to doing abdominal surgery. The fact remains, however, that in these days of simpler procedures most of us will hesitate about employing the Baldwin operation because it carries with it the inevitable operative risk of any such major operation.

There is one precaution which I should like to stress, when operations for absence of the vagina are contemplated. One should make sure that the vagina is really absent, as I have seen several cases in which the perineal body was entirely solid behind what appeared to be the urethral meatus, but in which a vaginal canal was present, opening into the urethra a short distance above the meatus. This is not an infrequent finding in pseudohermaphroditism, and the practical point in such cases is to make certain that a cystoscopic or endoscopic examination is done. The recognition of this condition is of great importance to the patient, because the surgical problem is a far simpler one than the construction of an artificial vagina. All that is necessary in cases of this type is to open the perineal body, dissect loose the posterior vaginal mucous membrane, and suture it to the perineal skin.

DR. BENJAMIN P. WATSON, New York, N. Y.—No mention has been made yet of a bloodless method of making an artificial vagina. I have under treatment at present a case in which this is being attempted. This patient first came to me about six years ago when she was 14 years of age because of severe abdominal pain recurring and ultimately becoming continuous. Believing her to have an imperforate vagina her physician had made an incision in the perineum and found retained blood.

On examination a definite swelling was found on one side of the pelvis with no vagina or vulvar orifice. It was evident that she had a rudimentary uterus, and on opening the abdomen this was found to be the case. The usual band going across the middle of the pelvis was present, at one side a swelling about the size of a pigeon's egg; and on the other side a rudimentary horn. The tubes and ovaries were normal on both sides. The rudimentary horns were each removed.

The patient being now 20 and contemplating marriage, she came for consultation with regard to the construction of the vagina. From the previous incision made between the urethra and rectum in an attempt to reach the retained menstrual fluid, there remained a shallow depression. The treatment consisted simply of supplying the patient with a glass vaginal dilator and instructing her to push this into the depression in the vulvar region, attach a T-bandage to it and wear this over night. We have gradually increased the size of the dilators and today, two months

after the initial treatment, she has a vagina into which a dilator can be introduced without pain for 3½ inches. I feel that with continuation of this treatment and marriage very soon, this patient probably will have a functioning vagina.

DR. LUDWIG A. EMGE, San Francisco, Calif.—The technique described by Dr. Falls is very ingenious, but it makes no provision for a desirable depth of the artificial vaginal canal. My experience with various methods has taught me that it is absolutely essential to eliminate the connective tissue ridge which traverses the pelvis at a right angle in the region of the uterine "anlage." This ridge has to be severed by sharp dissection and the rudimentary uterine vessels ligated.

Ordinarily this is not done except possibly with the Baldwin technique. Failure to do this usually results in a vagina of about two and one-half inches which is not an adequate length under certain circumstances. It is for this same reason, I believe, that Frank's invagination method only produces short vaginas.

Recently I have adopted the Wharton technique and of the 4 patients operated upon 3 had a vagina of from 4 to 6 inches in length, as demonstrated by these lateral views of x-ray studies. In the first case I failed to appreciate the importance of the uterine ridge and the result was a short canal. The Wharton technique is extremely simple, requires only two to three days of bed rest, and eliminates the necessity of skin transplantation. Epithelization can be hastened considerably by the nightly introduction of estrogenic suppositories. The vaginal canal usually develops a firm, normal-appearing mucosa in from two to three months. I allow my patients to wear a well-fitting balsa wood plug covered with a rubber membrane for about six weeks. No other treatment is necessary, and there is astonishingly little discomfort or vaginal discharge.

DR. JAMES R. MILLER, Hartford, Conn.—Estrogenic hormones, it should be borne in mind, have a reaction only upon tissues of Müllerian origin. Response to them can be expected in the method that Dr. Falls has utilized, but if vulvar skin is used one would not expect any effect.

DR. FALLS (closing).—As to the question of cooperation on the part of the patient in using the obturators, I have not had the difficulties that Dr. Masson has referred to. Particularly in the young married couples one finds it very easy to get cooperation.

The mortality in the Baldwin operation is, of course, the greatest deterrent. The irritating discharge following it has also been a source of complaint in the experience of nearly every man who has performed this operation.

Estrogen is apparently not necessary. The skin at the edge of the vagina supplies plenty of epithelium and while estrogen may hasten its growth, it is certainly not necessary.

The bloodless method demonstrates what can be done by simple pressure. I do agree that it is absolutely unnecessary to cut clear to the peritoneum in order to get a vagina that will be long enough for normal cohabitation. The danger of this bloodless method, however, may be a partial prolapse such as occurred in our case in which the vagina was formed from the pressure of normal intercourse.

(The Presidential Address of Dr. F. L. Adair will be included in the December issue.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Sterility

Stein, Irving F.: Further Studies in Infertility and Sterility, Surg. Gynec. Obst. **67:** 731, 1938.

An analysis of 200 childless couples examined in private practice showed that infertility was more frequently encountered than sterility. The male partner was responsible for about one-third of reproductive failures. Roentgenographic methods were of material value in investigation of the female partner. Pregnancy occurred in almost half of the matings in the infertility group and in only 15.4 per cent in the sterility group after investigation and treatment. Successful treatment in the infertility group was chiefly attributable to cervical cauterization, patency tests, and sex adjustments. In the sterility group, hormone therapy in the male and surgical treatment in the female were at times successful.

WM. C. HENSKE

Daniel, C., Mavrodin, D., and Waneff, A.: Research on the Permeability of the Tubes in Adnexal Inflammation, Gynécologie **37:** 15, 1938.

The investigations of the authors lead them to maintain that the tubes are patent in cases of adnexal inflammation more frequently than is generally believed. In their cases they found the tubes open in 43.2 per cent. One tube was permeable in 24.3 per cent; whereas both tubes were open in 13.5 per cent. Tubal insufflation succeeded in opening the tubes in 5.4 per cent of instances of adnexitis. In two cases of post-partum and postabortal pelvic cellulitis, the tubes were patent, indicating that inflammation of the cellular tissue leaves the tubes intact and does not predispose to sterility. The authors maintain that tubal insufflation in cases of adnexal infections, when carried out correctly and prudently, is a harmless procedure even when the infection is acute or subacute.

J. P. GREENHILL

Palmer, Pulsford, and Christeas: Hysterosalpingography With Fluid Lipiodol, Bull. Soc. d'obst. et de gynéc. **27:** 127, 1938.

One of the properties of ordinary lipiodol is its viscosity which has certain advantages and some disadvantages. The authors recently substituted fluid lipiodol, and they report their experiences with this type of lipiodol in 43 cases. They found the fluid lipiodol to be satisfactory in every way. In fact the x-ray pictures more truly represented the conditions looked for. The fluid lipiodol is well tolerated by the tissues and is more quickly absorbed than ordinary lipiodol.

J. P. GREENHILL

Held, E.: Occlusive Action of Lipiodol on Closed Fallopian Tubes. Contribution to the Study of the Origin of Foreign Body Tubercles in the Tube, Rev. franç. de gynéc. et d'obst. **34:** 489, 1939.

It is not the purpose of this communication to report on the inflammatory complications which occur after hysterosalpingography because every one knows of these. Held limits his remarks to the disturbances brought about within the

Fallopian tubes due to the presence of a foreign body which is injected. He reviews the literature and mentions a number of instances of such complications. He reports a case in which in a sterile woman, with closed tubes, hysterosalpingography was performed. One tube had to be removed after this procedure because an adnexal inflammatory mass developed. Microscopic examination revealed an old chronic salpingitis with tubercles of foreign bodies. Hence, the author agrees with Rubin who cautioned that circumspection be used in the injection of lipiodol in cases where the tubes are closed. In the opinion of the author the chief indication for hysterosalpingography is in cases where the tubes are closed and operation is contemplated. The author agrees with Dannreuther that tubal insufflation should be the test routinely performed in cases of sterility and that the use of iodized oil should be restricted for special cases. Insufflation by the Rubin kymograph method will greatly restrict the indications for the use of iodized oil injections.

J. P. GREENHILL

Walther, O.: The Question of Embolism During Hysterosalpingography With Lipiodol, Acta radiol. **20**: 457, 1940.

On hysterosalpingographic inspection it is sometimes found that the contrast fluid employed has entered the veins of the uterus and the pelvis. From there, the lipiodol is carried with the blood stream, via the common iliac vein, to the inferior vena cava, and thus for a short time becomes roentgenologically visible as a broad band parallel to the spinal column. Later, the iodized oil sticks in the arteries and capillaries of the lung, where it rapidly splits up into its two principal components, oil and iodine. Most of the iodine becomes excreted in the course of the first six to eight days, chiefly through the kidneys. Occasionally, when considerable quantities of lipiodol are injected directly into the vascular system, they may give rise to severe complications, or even be fatal, unless the now well-known precautions are duly observed.

J. P. GREENHILL

Laffont, A., and Bourgarel, R.: Sterility and the pH of the Masculine and Feminine Secretions, Bull. Soc. d'obst. et de gynéc. **27**: 221, 1938.

The authors investigated the pH of the semen, vaginal secretions and cervical secretions of sterile couples. All of the examinations were made during the intermenstrual interval. Among the 12 cases reported, there was one case in which the semen had a pH of 8.2. All the others were less than this. The pH of the vaginal secretion was fairly constant and ranged around 4.5. On the contrary the pH of the cervical secretion varied considerably and this variability fluctuated according to the pathologic condition which was present. The authors believed that to overcome sterility it is necessary to overcome the excess alkalinity of the cervical secretions and not its acidity as is commonly believed.

J. P. GREENHILL

Williams: The Relation of Sperm Motility to Fertilizing Ability, Urol. & Cutan. Rev. **43**: 587, 1939.

Motility is not prima facie evidence of fecundity. Motility is a function of the appendage, and does not indicate with any degree of certainty the condition of the sperm head, and its ability to unite with the ovum. It is an essential function of the healthy sperm if it is to migrate in the female genital tract and cause impregnation, but it is likewise an inherent characteristic of most spermatozoa that are not fit for impregnation purposes.

Spermatozoa are very sensitive to changes in hydrogen ion concentration, motility being impaired by slight changes in either direction. Ordinarily the hydrogen ion concentration of semen is about 8.1 to 8.4. The vagina has a pH of about 3.6 to 4.5, which would be incompatible for spermatozoa were it not for the

fact that the volume of seminal fluid is ordinarily sufficient to overcome any unfavorable acidity during the brief period of time when such might be a factor. Survival of the spermatozoa is fostered by the increased alkalinity of the cervix, uterus, and tubes, forming in consequence a physiochemical gradient in which the sperm is caused to travel in the direction of the most favorable environment. In the cervix, uterus, and tubes, the hydrogen ion concentration is usually in the neighborhood of 8.6.

One might expect that an increased alkalinity of the vagina would seriously interfere with the migration of spermatozoa by an alteration in the potential, aside from the fact that the inflammatory process behind the altered pH might in itself interfere with sperm migration. In the opinion of Williams, conception following alkaline douches is more likely to be due to the cleansing effect than to the contained alkali.

The degree of motility is tempered by metabolism of the sperm, which utilizes either a small amount of stored energy or energy derived from the surrounding medium. If kept at a temperature which is low enough to impede motility, the survival time is greatly increased. This is apparently due to the fact that spermatozoa contain a certain amount of stored energy which within a few hours is utilized if stimulated by heat, and which is conserved by cold. Spermatozoa will retain their motility longest if kept in a refrigerator at about 8° C., but at ordinary room temperature (about 20° C.) will often be alive and highly active after two or three days. Motility is but little affected within the first two to four hours at room temperature.

The following procedure is suggested as a convenient routine method of making motility examinations of in vitro specimens:

1. Obtain semen samples by ejaculation directly into wide-mouthed bottles, after which the bottle is tightly corked and kept at room temperature (15° to 20° C., or 60° to 70° F.).

2. Within two hours after ejaculation, examine for motility, noting the abundance of cells, the ratio of motile cells and the degree of motility. A note should also be made of the presence of any leucocytes. For this observation, a drop of semen is placed on a microscope slide, covered with a cover slip and examined at room temperature. If no motility is present or if motility is sluggish, the specimen is warmed to about 37° C. and re-examined. This will often induce or accelerate motility.

3. Re-examine at eight- to twelve-hour intervals until motility has ceased. In the normal cases, motility of some of the cells should endure for two or three days.

J. P. GREENHILL

Laffont and Bourgarel: Association Between the Biologic Action of the Cervical and Vaginal Secretions on Spermatozoa, Bull. Soc. d'obst. et de gynéc. **28**: 337, 1939.

In 34 sterile couples, the authors tried to determine whether there was any connection between the cytobacteriologic aspect of the cervical and vaginal secretions and their action on spermatozoa. They found that parasitic and bacterial infections of the vagina and urine prevent the normal activity of spermatozoa in the genital tract in two-thirds of the cases. On the other hand, in one-third of the cases, bacteriology does not explain the harmful effect of the vaginal and cervical secretions on spermatozoa and hence the authors turn to biologic incompatibility as the explanation.

J. P. GREENHILL

Watson, M. C.: The Effect of Cervical Secretions on the Vitality of Spermatozoa, Canad. M. A. J. **40**: 542, 1939.

The author believes that deficient cervical secretion, tenacious mucus plugs in the cervix, and mild inflammation of the cervix present conditions hostile to the invasion of healthy spermatozoa. In a small series of sterile patients in which

one or more of the above were the only demonstrable abnormalities 100,000 to 150,000 international units of estradiol benzoate were given intramuscularly forty-eight hours previous to postcoital examination. He reports a definite increase in the amount of secretion available for examination, with a very marked increase in the number of actively motile sperm which could be recovered. He suggests this effect as a mechanism by which estrogenic stimulation may prove effective in some cases of sterility.

CARL P. HUBER.

Moench, G. L.: The Relation of Certain Seminal Findings to Fertility, With Special Reference to Sperm Concentration and the Significance of Testicular Epithelial Cells in Semen, Am. J. Surg. **47**: 586, 1940.

The number of sperms produced ordinarily is far in excess of that needed to fertilize the ovum. Very long, tapering and narrow sperm heads are of especially sinister import and their shortening is often the first sign of improvement. By evaluating the clinical data, the sperm morphology and the presence and number of the protoplasmic drops and seminiferous epithelial cells, it is frequently possible to distinguish between sexual fatigue, testicular hypoplasia, and acute and chronic testicular tubule degeneration.

J. THORNWELL WITHERSPOON

Eastman, Guttmacher and Stewart: Experimental Observations on "Sperm Immunity" in the Rat, J. Contraception **4**: 147, 1939.

The "sperm immunity" theory is based on the idea that parenterally injected semen produces specific antibodies (spermatoxins) which are lethal to spermatozoa introduced into the female genital tract. Such immune bodies, chiefly precipitins, actually develop in the blood sera of rats, as established by reliable investigators. However, in regard to the second implication of this hypothesis, namely, temporary sterility, seemingly convincing evidence has been advanced both in favor and against this resulting effect.

Thorough reinvestigation of this latter problem by the authors leads them to the conclusion that in white rats a slowly progressive decrease in fertility begins at the age of 12½ months, probably accounting for the seeming success with sperm injections in some experiments.

When one compares, age by age, the fertility of injected animals with the controls, it appears that parenteral injection of live sperm reduces slightly the fertility of the recipients, but the reduction is neither of significant degree nor of practical importance.

HUGO EHRENFEST

Dickinson, Robert L.: An Ensemble for Ovulation, J. Contraception **3**: 219, 1938.

Dickinson from an analysis of a huge amount of material concludes that there is a "safe" period during the week preceding menstruation which, without protection, is as safe from conception as is intercourse guarded by any method except two. These are the condom, consistently tested before use, and the skillfully fitted pessary-with-jelly, unfailingly used.

It is the week following the period and during the period itself, in which his maze of assembled notes casts grave doubt, if not actual denial, of safety or sterility.

J. P. GREENHILL

Chalier, A.: Total Linear Salpingostomy for the Treatment of Tubal Sterility, Bull. Soc. d'obst. et de gynéc. **27**: 242, 1938.

In the opinion of Chalier tubal disturbances account for about one-half of the cases of sterility in women. In mild cases, conservative measures may be used

to overcome the local abnormalities; but in severe cases, surgery must be employed. Among the surgical procedures used to overcome tubal obstruction, the author mentions (1) salpingolysis, liberation of the adherent tube, (2) salpingostomy, the formation of an artificial opening in the tube, (3) partial salpingectomy, (4) subtotal salpingectomy with tuboovarian fixation, and (5) tubal implantation where the proximal part of the tube is removed and the rest of the tube implanted into the uterine cavity. He recommends an operation called total linear salpingostomy whereby the tube is cut open for its entire length from the fimbriated to the cornual end. He reports one patient operated upon by this method with a subsequent pregnancy.

The advantages of this operation are the saving of the entire tube and the maintenance of its normal blood supply and innervation. The operation is also excellent treatment for salpingitis, especially of tuberculous salpingitis.

J. P. GREENHILL

Villard: Salpingostomies in the Treatment of Sterility, Bull. Soc. d'obst. et de gynéc. **27:** 285, 1938.

Among the cases of salpingostomy performed by him, two patients had miscarriages but one had three pregnancies. In all, five living children were delivered. The author points out that the cases in which pregnancy occurred after salpingostomy were those in which the etiology of tubal closure was a puerperal infection. He did not encounter a single successful result in the gonorrheal cases.

J. P. GREENHILL

Robecchi, E.: Radiology in Female Sterility, Ginecologia **6:** 1, 1940.

The author discusses the diagnostic pneumoperitoneum and its combination techniques, colpography and hysterosalpingography. His findings in 500 cases of female sterility having salpingographic studies are presented. Nearly one-third in this series were revealed to have normal tubal patency; 40.7 per cent evidenced bilateral tubal occlusion; 8 per cent unilateral tubal nonpatency; and 4.4 per cent were found to have a functional tubal occlusion.

The author lists nine complications that may occur incidental to hysterosalpingography. There are the various reactions of the Fallopian tubes to the introduced pressure used during the technique, peritoneal reaction to the iodized oil, penetration of the iodized oil into the blood vessels and lymphatics about the tubes and uterus, actual perforation of the uterine wall, late pain, endometriosis, ovarian damage from the roentgen rays, iodism, and last the interruption of an early pregnancy.

In the latter part of the article the writer discusses radiology as therapy in the treatment of female sterility. The author notes that pregnancy followed hysterosalpingography 31 times, and of these 2 were ectopic pregnancies. In conclusion, Robecchi discusses roentgenotherapy of the ovaries, hypophysis, thymus, and thyroid glands.

CLAIR E. FOLSOME

Glober, L. J.: The Treatment of Sterility, South. M. J. **31:** 981, 1938.

There is involuntary sterility in at least 15 per cent of marriages. A complete history of the couple and a thorough physical examination of the wife are essential preliminaries in a solution of the problem. The investigation is facilitated by a consideration of four factors:

(a) *Male Factor:* Includes a careful history, and a detailed examination of semen obtained after a period of continence of approximately a week's duration. Moench and Hotchkiss' standards for male fertility have minimal requirements of normal viscosity, a volume of at least 1 c.c., with a sperm count of at least 60,000,000 per c.c., with less than 18 to 20 per cent of abnormal sperm.

(b) *Constitutional Factors:* The so-called "index of fertility," which depends upon the strength of the germ plasm, may be lowered by the presence of an anemia, obesity, marked malnutrition with vitamin and mineral deficiency, sexual excesses, syphilis, tuberculosis, and worry. Appropriate corrective measures should be instituted.

(c) *Mechanical Factors:* These prevent the union of the male and female germ elements. Approximately one-third of sterile women have diseased cervices. The ingredient of human sperm which causes lysis of a normal cervical plug is interfered with when pus is present. Failure of the cervix to dip into the seminal pool requires postural treatment during and after coitus.

The indications for artificial insemination are: (1) Effluvium seminis; (2) rare cases of persistent endocervicitis; (3) failure of cervix to contact seminal pool; (4) rarely, when the specimen is fertile but deficient in amount. The procedure must be performed with aseptic precautions, and it is best done just before ovulation.

Tubal patency should be tested by the Rubin test or salpingohysterography. Operative procedures on the tubes may occasionally be indicated, but these are not often attended with success.

(d) *Endocrine Factors:* In the less obvious endocrinopathies these factors may be somewhat difficult to determine. In addition to the quantitative biologic tests when they are available, basal metabolic rate, glucose tolerance tests, and endometrial biopsies frequently offer useful information. Endocrine treatment is not standardized, and a number of agents are employed. The author expresses preference for thyroid extract, claiming that it apparently improves germ plasm of both sexes.

Mention is made of three patients in whom spermatoxins were believed to have been responsible for the sterility. In a hanging drop, a saline suspension of sperm and wife's serum caused agglutination.

ARNOLD GOLDBERGER

Berutti, Enrico: The Etiology and Basis of Effective Therapy in Human Sterility, Ginecologia **6**: 99, 1940.

The first center for the sole study and treatment of sterility in Italy was established at the University of Torino. The author, in a footnote, states that the activities of this clinic were of particular interest to Il Duce.

The writer offers a long statistical paper on the 1,050 infertile and sterile patients seen at the Torino Sterility Center. Of this group, 742 were diagnosed as having primary sterility, 288 classified as secondary sterility and another 20 instances gave an uncertain history of preceding menorrhagia.

Hypoplastic uteri were found in 221 cases of the 742 instances of primary sterility. The 3 major pathologic situations presented by gynecologic examination in the primary sterility group were cervical erosions (9.43 per cent), cervicitis (7.28 per cent) and uterine retroversion (8.49 per cent). Eighty cases (10.78 per cent) of the primary sterility series gave a history of previous laparotomy.

In the 288 cases of secondary sterility, it was observed that in 127 instances the sterility followed a single abortion while in 83 other cases it followed the first pregnancy. The 3 major diagnoses in this second group were: metroadnexitis (14.21 per cent), hypotrophic uterus (11.8 per cent), and endometritis and metritis (10 per cent).

Tubal patency tests were performed in 400 individuals and in 31.5 per cent both tubes were patent; in 40.2 per cent both tubes were found occluded, while in only 8 per cent the tubal occlusion was limited to one tube. The remaining cases evidenced functional occlusion, reduced or doubtful tubal patency. In 25 cases (6.25 per cent) showing tubal changes, a pregnancy followed hysterosalpingography. Pregnancy occurred in 11.9 per cent of the total 400 cases, but this latter figure includes the 126 instances showing normal tubal patency.

The large series of cases investigated under such ideal conditions make the author's study a worth-while contribution to the problem of sterility.

CLAIR E. FOLSOME

Item

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held in June, 1941.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, from May 28 to June 1, 1941, immediately prior to the opening of the annual meeting of the American Medical Association.

Application for admission to Group A (Part II) examinations must be on file in the Secretary's Office not later than March 15, 1941.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

The Board wishes to announce a modification of the case record ruling (effective January 1, 1942) as it appears in the September, 1940, issue of the Board booklet. This ruling should read: "It is preferable that the number of cases submitted should not be more than half (25) of the total number of fifty (50) cases required."

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

BACILLARY AND RICKETTSIAL INFECTIONS. By William H. Holmes, Professor of Medicine, Northwestern University Medical School, etc., Chicago. The Macmillan Company, New York, 1940.

SEX IN DEVELOPMENT. Edited by Carney Landis, Associate Professor of Psychology, Columbia University; Principal Research Psychologist, Psychiatric Institute and Hospital. 329 pages. Paul B. Hoeber, Inc., New York, 1940.

CIRUGIA DE LA CONSTIPACION. Par el Dr. Conrado Zuckermann, professor de patologia quirurgica de la faculdad de medicina de Mexico. Con 32 grabados. Mexico, 1939.

THE ANATOMY OF THE FEMALE PELVIS. By F. A. Maguire, Honorary Lecturer in Anatomy; Honorary Gynaecological Surgeon, Royal Prince Alfred Hospital, and Prince Henry Hospital in Sidney. Third edition, 162 pages, illustrated. Angus and Robertson, Sydney, Australia, 1940.

EXPECTANT MOTHERHOOD. By Nicholson J. Eastman, Professor of Obstetrics, Johns Hopkins University, and Obstetrician-in-chief, Johns Hopkins Hospital. 176 pages, illustrated. Little, Brown and Company, Boston, 1940.

PHYSIOLOGY OF THE FETUS. By William Frederick Windle, Professor of Microscopic Anatomy, Northwestern University Medical School. 249 pages, illustrated. W. B. Saunders Company, Philadelphia, 1940.

RECENT ADVANCES IN SEX AND REPRODUCTIVE PHYSIOLOGY. By J. M. Robson, Lecturer in Pharmacology University of Edinburgh. With introduction by Professor F. A. E. Crew, Director of the Institute of Animal Genetics, Edinburgh. Second edition, 539 pages with 62 illustrations. Blakiston Company, Philadelphia, 1940.

ABDOMINAL OPERATIONS. By Rodney Maingot, Senior Surgeon to the South-End General Hospital, London, etc. In two volumes, 1385 pages with 298 illustrations. D. Appleton-Century Company, New York, 1940.